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SUCCESSFUL RESECTIONS FOR BILATERAL PULMONARY ARTERIOVENOUS FISTULAS*

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ALTHOUGH pulmonary arteriovenous fistulas were first reported in 1897 by Churton[1] the significance of these lesions has been overlooked until recent years. The first report of a case diagnosed clinically with certitude was made in 1939 by Smith and Horton,[2] and in the same year Hepburn and Dauphinee[3] described for the first time the surgical treatment of these lesions. In 1946 Lindgren[4] wrote one of the early reports of the x-ray manifestations of pulmonary arteriovenous fistulas. There are now over 150 cases reported in the literature, including the excellent description of the syndrome by Burchell and Clagett.[5] Nevertheless, pulmonary arteriovenous fistulas may still defy early recognition. This is particularly true of bilateral arteriovenous fistula of the lungs, reports of which are rare. In the classic American monogram on angiocardiography[6] no examples of bilateral arteriovenous fistulas of the lung were encountered. Reports of a successful bilateral resection of lung tissue containing pulmonary arteriovenous fistulas are even rarer. We therefore present what we believe is the third reported case of a patient successfully treated by bilateral lung resection to eradicate pulmonary arteriovenous fistulas. The papers of Adams[7] and Behrend and Baer[8] constitute the only others of which we have knowledge.

CASE REPORT

A 62-year-old housewife was admitted to the University Medical Service of the Kings County Hospital on November 26, 1954, because of anemia. On July 10 she had had an attack of melena for 8 days. She had previously been in good health except for a cholecystectomy and a partial gastrectomy performed several years earlier for a duodenal ulcer.

Physical examination showed a well developed and well nourished woman. The only abnormal signs were small telangiectases on the right buccal mucosa and conjunctivas of both eyes.

The temperature was 99°F., and the pulse 80. The blood pressure was 125/80.

The hemoglobin was 6.5 gm. per 100 ml. on admission and 9.5 gm. per 100 ml. after a blood transfusion of 1000 ml.

On the day after admission, what was at first thought to be an acute psychosis developed. Coma and nuchal rigidity occurred. A lumbar puncture showed many red blood cells and xanthochromic spinal fluid. Because of these findings a diagnosis of subarachnoid hemorrhage was made. The patient improved gradually after this episode. Roentgenograms demonstrated a duodenal ulcer and a circumscribed density in the left-middle-lung field. She was therefore transferred to the Pulmonary Disease Section for further studies, with a tentative diagnosis of tuberculosis or pulmonary neoplasm. A history of mild dyspnea and slight fatigue on exertion for many years was now obtained for the 1st time, and examination revealed a continuous systolic and diastolic bruit over the left-middle-lung field anteriorly and in the axilla, and over the right anterior aspect of the chest in the midclavicular line near the diaphragm. No neurologic residua were noted.

The hemoglobin had now fallen to 4.5 gm. per 100 ml. The bleeding time was 45 seconds, and the clotting time 3.5 minutes. Urinalysis was negative. No blood was found in the stool. The blood urea nitrogen was 19 mg. per 100 ml., and the carbon dioxide content 58 vol. per cent. The serum chloride was 110 milliequiv. per liter.

Because of the presence of telangiectasia and bilateral bruits over the lungs and the fluoroscopic findings of pulsation and change in size of the lesion on the left side, as well as the general x-ray signs described below, a diagnosis of pulmonary arteriovenous fistulas was considered. A posteroanterior roentgenogram of the chest (Fig. 1) showed a lobulated density in the left-middle-lung field. Extending from the hilar region to this density was a broad, vascular shadow. A similar shadow was detected in the right lung extending from the hilus to the diaphragm. A tomographic study barely delineated the lesion on the right side, but clearly showed the lobulated mass in the left lung. To clarify the diagnosis further, an angiocardiographic examination was performed. A posteroanterior view at 5 seconds definitely showed the left-sided density to be an arteriovenous fistula. The broad vascular shadow seen on the right side in the standard roentgenogram was seen in the angiogram to be composed of 2 distinct vessels communicating with a large pulmonary arteriovenous fistula situated at the level of the diaphragm (Fig. 2). A lateral view demonstrated the 2 lobulated arteriovenous fistulas, with the greatly enlarged afferent and efferent pulmonary vessels (Fig. 3). The lesion on the left side was located in the base of the anterior segment of the left upper lobe, and that on the right side was in the middle lobe.

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Pulmonary-function studies were reported as follows: vital capacity, 3057 ml. — 112 per cent of predicted value; maximum breathing capacity, 71.3 liters per minute — 128 per cent of predicted value; respiratory rate, 28 per minute; tidal volume, 636 ml.; inspiratory reserve, 2525 ml., and expiratory reserve 532 ml.; residual capacity divided by total lung capacity times 100, 34 per cent; ventilatory equivalent, 3.3; arterial oxygen saturation, 93.7 per cent at rest and 82.4 per cent after standard exercise; and arterial carbon dioxide, 35.6 vol. per cent resting and 36.4 vol. per cent after standard exercise. After inhalation of 100 per cent oxygen, the arterial oxygen saturation went from 94 per cent to 95 per cent.

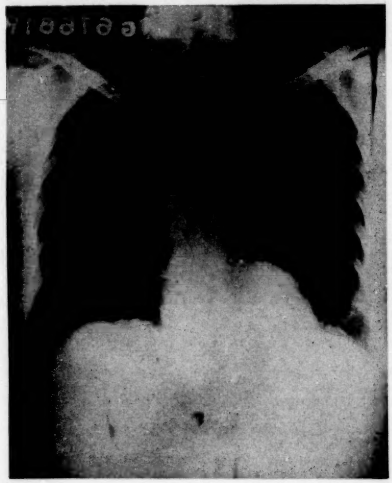


FIGURE 1. *Posteroanterior Roentgenogram, Showing the Slightly Lobulated Density Produced by the Arteriovenous Fistula in the Left-Middle-Lung Field.*

The vascular shadow running from the hilus to the fistula is somewhat obscured by the seventh rib posteriorly.

Because of the neurologic complication, the large size of the arteriovenous fistulas, the duodenal ulcer (which presumably may have been the result of previous polycythemia) and the anemia, surgical resection of the fistulas was recommended. The right middle lobe was resected on December 21. A large, thin-walled fistula was present on the pleural surface, which was bluish in color and tense in consistence (suggesting the possibility of imminent rupture). Injection of the surgical specimen with urokon outlined the enlarged pulmonary artery and vein communicating by way of the fistula (Fig. 4*A* and *B*). The postoperative course was uneventful. Seven days after operation, the hemoglobin was 13 gm. per 100 ml., the hematocrit 46 vol. per cent, and the red-cell count 4,430,000. Sixteen days later, the left upper lobe was resected to remove the contralateral fistula, which was located deep within the anterior segment. The distribution and size of the abnormal afferent and efferent vessels at the hilus of the lobe precluded a segmental dissection. The bruits over the lungs were no longer audible. Again, the postoperative course was uneventful.

Since the operations, the hemoglobin has been maintained at normal levels. In the angiograms taken eight weeks after operation, the pulmonary artery is enlarged; the arteriovenous fistulas, as well as their respective afferent and efferent branches of the resected portions of the lung, are no longer apparent (Fig. 5*A* and *B*).

Pulmonary-function studies, performed 8 months after the operations, were reported as follows: vital capacity, 2.31 liters — 78 per cent of the predicted value; maximum breathing capacity, 59.0 liters per minute — 82.3 per cent of the predicted value; respiratory rate, 20 per minute; tidal volume, 666 ml.; inspiratory capacity, 1.27 liters, and expiratory reserve, 1.04 liters; functional residual capacity, 2.75 liters; total lung capacity, 4.04 liters; residual capacity divided by total lung capacity times 100, 42 per cent; arterial oxygen saturation, 100 per cent at rest and 96 per cent after standard exercise; and arterial carbon dioxide content, 45.3 vol. per cent at rest and 42.3 vol. per cent after standard exercise.

The lower vital capacity and maximum breathing capacity were due to the loss of ventilating lung volume of the right middle and left upper lobes. There was considerable improvement in the arterial saturation and in the arterial carbon dioxide content, which showed a striking return to normal.

This case illustrates the facility with which pulmonary arteriovenous fistulas may be overlooked; the diagnosis was not made until after the patient had been transferred to the Pulmonary Disease Section.

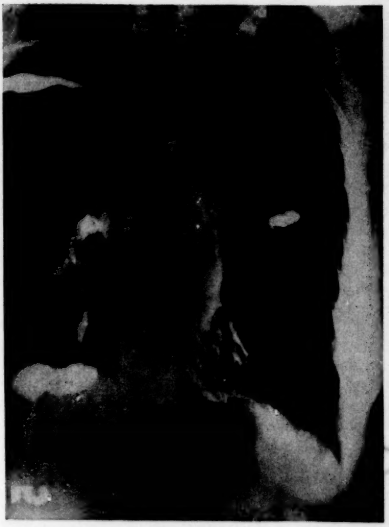


FIGURE 2. *Preoperative Posteroanterior Angiocardiogram at the Five-Second Interval, Establishing the Lesion As Pulmonary Arteriovenous Fistula.*

The afferent and efferent vessels can be seen on both sides. Note the large size of the components of the fistula lying at the level of the right hemidiaphragm.

Previously, bronchogenic neoplasm or pulmonary tuberculosis was considered the most likely diagnosis. The cerebral symptoms were attributed to some coexistent but as yet unidentified lesion. The probability of an etiologic relation between the lesions in the lung and the intracranial lesion causing the subarachnoid hemorrhage apparently was not considered. Because we believe that pulmonary arteriovenous fis-

tula frequently remains unrecognized, the outstanding features of this syndrome are reviewed here.

Symptoms and Signs

Cyanosis, clubbing of the fingers, polycythemia associated with dizziness in the absence of cardiac abnormality, dyspnea, syncope and dysarthria constitute the typical picture. More than half the patients have small capillary hemangiomas of the skin or mucous membranes. Such mucocutaneous telangiectases constitute a very important diagnostic sign. Half the patients have such findings of the Rendu–Osler–Weber syndrome so that a thorough examination of the skin, nail beds, ears, nose, throat, larynx and retina is strongly advocated in search of angiomas.

Cyanosis dominates the clinical picture. It is frequently present, but its intensity is variable. It may be present at birth, but often only becomes noticeable later in life, especially at puberty. Cyanosis may remain absent, especially if the shunt is small or if there is a bronchial-artery communication or some other anomaly, as in the cases reported by Lindskog et al.[9] and Watson.[10] The cyanosis may disappear after a hemorrhage and reappear after a transfusion.

Clubbing of the digits usually appears with cyanosis and often is quite marked. It is believed to be common as the first sign of a pulmonary arteriovenous fistula, and when it is present one should institute a careful search for this lesion.

Dyspnea is frequently associated with cyanosis and usually develops in later years. The dyspnea may be that of effort only, or may occur in paroxysms.

Hemoptysis may be very notable. The copiousness of the hemoptysis may, in certain cases, offer some clue to the prognosis. Epistaxis, at times, may be sufficiently voluminous to require transfusions or may manifest itself as repeated, less serious bleeding. Hemorrhages may arise from arteriovenous fistulas in the gastrointestinal tract, or as a result of duodenal ulceration, which is a common accompaniment of polycythemia. A massive hemorrhage may cause the disappearance of polycythemia, the absence of which may be erroneously interpreted as excluding a diagnosis of arteriovenous fistula.

Polycythemia is often found, with average red-cell counts of 6,000,000 to 9,000,000, or as high as 11,000,000 in exceptional cases.[11] The hemoglobin range on the average is 16 to 18 gm. per 100 ml. Occasionally, an anemia, unexplainable by the discovery of a source of a major hemorrhage, may be present. Such an anemia may be spontaneously corrected after surgical removal of the angiomas. There are cases in contrast to these in which neither anemia nor polycythemia is noted and in which the hemoglobin and red-cell count are normal.[9]

Thoracic pain may occur, sometimes long before the development of other symptoms.

The heart is, as a rule, normal. However, Sloan and Cooley[12] found cardiomegaly in 17 of 94 patients, in 8 of whom no cause for the enlargement other than the fistulas could be discovered. Yater[13] found cardiac signs in 9 out of 45 cases.

Auscultation of the lungs often reveals a bruit that is loudest in the region of the arteriovenous fistula. In Yater's[13] series of 45 cases, a bruit was present in 26. The bruit may be heard during both systole and diastole, or only during the systolic phase of the cardiac cycle. It is usually much louder during deep inspiration and is practically inaudible on expiration.

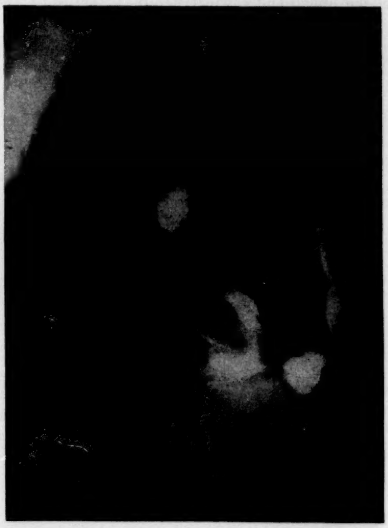


Figure 3. *Lateral Angiocardiogram, Showing the Arteriovenous Fistulas in the Base of the Anterior Segment of the Left Upper Lobe and in the Periphery of the Right Middle Lobe.*

The patient described above is an example of one who had dyspnea, mucosal hemangiomas, bilateral pulmonary bruits and a severe gastrointestinal hemorrhage that depressed the blood elements to anemic levels, and during the period of observation cyanosis was not detected. Polycythemia was absent for the same reason.

Radiologic Examination

A thorough x-ray evaluation of the chest will nearly always establish the diagnosis of arteriovenous fistula. We therefore consider this type of examination the most significant. Ordinarily, one or more unilateral or bilateral pulmonary opacities may be detected in the roentgenogram. However, the vascular nature of such shadows may not be recognized. Lesions at the pulmonary bases may be obscured by the diaphragm (as was true of the right-sided lesion in the patient

described above), and lesions in the medial portion of the left base may be obscured by the heart shadow. Often, the abnormal shadows may only be seen in a lateral or oblique roentgenogram. Fluoroscopy aids in the recognition of the true nature of the lesions by disclosing that they are pulsatile and have a definite connection via vascular shadows with the hilus of the lung. The vascular nature of the fistula and its communicating vessels may be demonstrated by the use of the Valsalva and Mueller maneuvers, a considerable decrease in the size of the lesions occurring with the former and a marked increase in size with the latter.

Tomography helps to localize the fistula and may delineate its afferent and efferent vessels, but will often fail, we believe, to make the distinction between vascular and avascular lesions. In the case reported above, tomography did not demonstrate the lesion in the right lower lobe.

Angiocardiography is the procedure that definitely establishes the diagnosis of pulmonary arteriovenous fistula. It is strongly advocated in all patients suspected of having such fistulas, because it conclusively demonstrates the vascular nature of the abnormal pulmonary densities, it may uncover smaller arteriovenous fistulas that otherwise would go undetected, and it provides an accurate localization of the lesions.

Physiologic Findings

The arterial oxygen saturation is usually decreased, but the inhalation of 100 per cent oxygen may elevate the level to almost full saturation when the fistula is small. The most interesting finding is the lowered arterial carbon dioxide tension.[14] In the case presented above, the value for the arterial carbon dioxide was 35.6 vol. per cent before and 45.3 vol. per cent after operation. The resting arterial oxygen saturation — 93.7 per cent — was reduced slightly, falling to 82.4 per cent after exercise. Repeated study with the inhalation of 100 per cent oxygen resulted in only a 2 per cent elevation of the arterial saturation. After operation it was 100 per cent saturated, falling to 95 per cent saturation after exercise.

When cardiac catheterization has been performed, normal or even reduced pulmonary vascular resistance has been observed. However, there are cases of increased resistance, which Giampalmo[15] explains as due to small thromboses in the pulmonary arteries or to arteriolar constriction. In addition to measure-

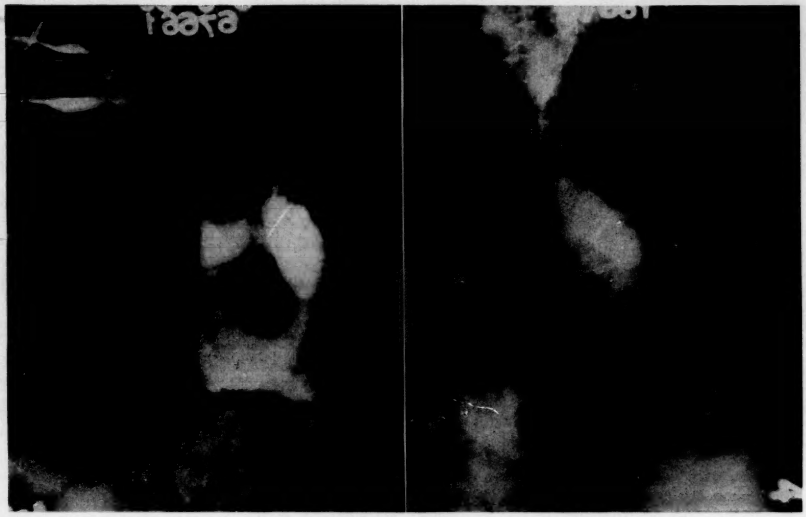
A B

FIGURE 4. *Posteroanterior* (A) *and Lateral* (B) *Views of the Resected Middle Lobe, Showing the Abnormal Vascular Channels and the Arteriovenous Fistula Filled with Radiopaque Medium.*

ment of resistance, the volume of the shunt through the fistula may be calculated by catheterization.

The electrocardiogram is usually normal. Occasionally, a right-axis deviation is noted, with or without ventricular strain; left-axis deviation may also be present. Conduction defects are rare and probably not due to the fistula. Donzelot et al.[16] have employed the cardiac catheter to determine the fistulas develop because of a stimulus similar to that which produces new mucocutaneous lesions in Rendu–Osler–Weber disease is speculative.

Early recognition of the arteriovenous fistulas is important because of the life-threatening nature of the complications, which include hemorrhage, infection and thromboembolic lesions. Severe hemorrhage, sometimes induced by exertion,[19] may arise in various



A B

FIGURE 5. *Posteroanterior* (A) *and Lateral* (B) *Angiocardiograms Three Months after Operation. No arteriovenous fistulas are seen.*

circulation time with ether injected into selected areas of the lung. Normally, ether is volatilized as it passes through the pulmonary vascular bed. In the presence of pulmonary arteriovenous fistula, however, sufficient liquid ether is shunted to the systemic circulation to give rise to paresthesias, localized hyperemia and other responses that constitute a positive test. The method is hazardous, and was not employed for the patient described above.

PROGNOSIS

The prognosis depends upon the course of the disease, the development of complications and the presence or absence of associated lesions.

Pulmonary arteriovenous fistulas may cause difficulty in early life, or, as in the case reported above, may not become manifest until the sixth decade.[17,18] According to Lindskog,[9] there may be progressive development of arteriovenous fistulas. Whether new sites. Fatal intrapleural[20-23] and pulmonary[7,24,25] bleeding has been described. Frequent attacks of otherwise unexplained epistaxis in the presence of a pulmonary lesion suggest the likelihood of pulmonary arteriovenous fistula and Rendu–Osler–Weber disease. Hemorrhage may occur from any of the mucous membranes. Hedinger and Hitzig[25] reported its occurrence from the tongue. Gastric or duodenal hemorrhage may be the presenting symptom of the disease, the cause being a mucosal varix or duodenal ulcer; the latter lesion is a typical complication of polycythemia and is common in patients with pulmonary arteriovenous fistula, as is illustrated by this report. Infection may manifest itself as a cerebral abscess, endocarditis or infection in the walls of the fistula. Thrombosis is frequent because of the polycythemia. When it involves the cerebral veins, hemiplegia may result. Air emboli have been postulated as occurring and Lindgren[4] observed bubbling in a pulmonary arteriovenous fistula at operation.

Cardiac anomalies such as interventricular, interatrial and aortopulmonic defects have been reported in association with pulmonary arteriovenous fistulas.[19,26,27] Although uncommon, the presence of such associated abnormalities adversely affects the prognosis.

Treatment

Resection of the lung tissue containing the fistulas is the only effective method of therapy. The number and location of the lesions may preclude complete ablation because too great a sacrifice of one tissue may be necessary. It may be for this reason that bilateral pulmonary resection for arteriovenous fistulas has rarely been reported, the present case representing the third example. The patient of Behrend and Baer[8] needed three separate resections with removal of both lower lobes and lingula before clinical improvement occurred. Adams[7] and Behrend and Baer[8] performed several operations on the same patients. The use of local resection of the fistula or multiple segmentectomies may offer some hope in the future for a larger number of surgically treated patients with bilateral lesions. Emergency thoracotomy may be needed for the patients who have massive hemoptysis or intrapleural hemorrhage.

The extent of the lesions or other compromising situations are the only contraindications to surgical treatment. Age is not a contraindication — the patient described above was sixty-two years old.

Summary

The case of a sixty-two-year-old patient with bilateral pulmonary arteriovenous fistulas, who had a gastrointestinal hemorrhage and severe neurologic symptoms, and who was treated by bilateral pulmonary resection, is presented. We believe this to be the third reported case of bilateral resection for this condition.

The patient's health improved considerably after the operations.

A discussion of the history, diagnostic signs, physiologic disturbances and radiologic findings of pulmonary arteriovenous fistulas is included. We believe that the large majority of pulmonary arteriovenous fistulas should be resected, the only specific contraindications being associated irreversible pulmonary insufficiency and too extensive a distribution of the lesions to permit total resection.

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PSYCHIATRIC CONSIDERATIONS IN THE ADJUSTMENT OF PATIENTS WITH POLIOMYELITIS*

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No two orthopedic conditions are ever exactly the same to the last detail, nor do any two patients ever show precisely the same array of symptoms. Yet there are essential similarities in symptom patterns that enable the physician to think of one patient as being much like others in his experience and allow him to distinguish meaningfully one group of patients from another. In large measure this patterning is the key to all diagnosis and treatment. In a general way paralytic poliomyelitis resembles a large number of other orthopedic conditions, both as an illness experience for the patient and as a problem in treatment and management for the physician. Like fractures, poliomyelitis is characterized by a rapid onset; it is an infectious disease like osteomyelitis or tuberculosis, as well as a crippling disease requiring lengthy hospitalization. The patient is often immobilized for some time; he is given various kinds of physiotherapeutic treatment, and with other orthopedic patients he shares a familiarity with casts, braces and other orthopedic appliances. Likewise, as with other orthopedic patients, hospitalization and treatment are centered on a somatic change, an insult to the musculoskeletal system.

Any orthopedic intervention stems from the physician's conviction that, for a given patient, a particular procedure is the most appropriate and efficient way to correct a muscular impairment, to prevent crippling or to apply support. When the physician decides to prescribe a brace, the meaning of this appliance for him, and his expectations of its probable efficiency, rise out of his appraisal of the totality of medical considerations of the case. The meaning that the patient gives to the brace — what he thinks about it and how he believes it is going to work for him — may differ sharply from the significance of the procedure as perceived by the physician. For the patient the brace may have a unique and private meaning; the members of his family may think about it in still different ways. In effect, everyone who is concerned with the progress of the patient may have his own standards on which to base his judgment about what is going on. To some degree this is to be expected. In assessing the condition of his patient, the orthopedic surgeon brings to bear the full range of his professional conviction, training and experience. Only marginally can the patient and the patient's family share the scientific knowledge of the physician; often they are able to share some of his goals, but they also must act and react according to their own feelings, which often distort medical knowledge in very curious ways. Poliomyelitis — even the word itself — is loaded with emotion for most people. Especially in situations of stress and anxiety, lay misconceptions show amazing strength and persistence; it is difficult for many people to give them up. Some time ago a mother whose adolescent son had a residual paralysis from poliomyelitis was interviewed at length on several occasions in connection with a research investigation. This mother, a woman of average intelligence, had consulted many doctors, had read a good deal about poliomyelitis and in general had tried to acquire as much information as possible about the disease. When asked to tell how she thought her son had contracted poliomyelitis, her reply was: "This may be a stupid theory of it, but I really think it comes from milk." She went on to describe a violent altercation she had had with her milkman. "Don't you leave me any more of your milk." When the milkman asked why, she said, "Look at my son. He's crippled from your milk. If I had any more children I would make them drink soda pop instead of milk."

More recently a series of interviews has been conducted with a patient with spinal poliomyelitis, an eleven-year-old boy who was infected in September, 1954, and who has a severe involvement of a lower extremity. During the fall months the patient's convalescence progressed satisfactorily, and in January the physician prescribed a brace and arranged for the patient to get out of bed. The brace was duly fitted and seemingly accepted by the patient, who forthwith became ambulatory. But the boy ascribed a curious and baffling meaning to his brace: "When you're down in bed it's a sign that you're improving. If you start getting up you're not improving as much as you did before." He went on to say, "Well, when you start getting up they put a brace on you. But if they keep you down and you're still improving, then you won't have to have a brace after a while. If you get a brace you'll be able to go home sooner instead of staying here in the hospital and really getting better." Here the physician prescribed an appliance after

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some muscle recovery, but to this youngster the brace was clearly a symbol of failure, an indication that he had not improved and would not. In our experience, this is not an unusual observation, and it suggests that, at least in some cases, the physician's ability to get the patient to use an appliance properly will be increased by an understanding of the meaning of the appliance to his patient.

If a pathologic process is to be studied from the point of view of hospital adjustment and rehabilitation, such considerations as these suggest that the investigation must be broad in scope. It is not enough to observe the patient alone, or to study the relation between the patient and his doctor. The patient is certainly the core figure, but there are many influences that bear upon him and his illness. For the patient, the experience of the disease is a collection of environmental changes and interventions of various kinds, and many people deal with him throughout — the nurses, the physiotherapist, his doctor and members of his family, among others. It is also our experience that such a study must be long in term, with many repeated observations and interviews, if valid results are to be obtained. It is commonly found, for example, that only after a relation with a patient has been well established for some time will he feel free to disclose some of the problems that really concern him, or express negative feelings about his treatment, the hospital, or his doctor.[1,2] In briefer contact this sort of material may not be found at all.

Method of Study

This is a progress report of a study of a group of children with spinal poliomyelitis, all with some degree of lower-extremity involvement. The investigation is being conducted at the Psychiatric Institute, University of Maryland School of Medicine, by a research team that includes a number of different professional disciplines: psychiatry, pediatrics, sociology, psychology and psychiatric social work. The purpose of the study is to investigate some of the circumstances or factors that appear to contribute to the ways patients and their families react and adjust themselves to the total experience of the disease and its sequelae — to come to some clearer understanding of the mechanics of the changes that seem to take place in their lives. The method is that of longitudinal investigation, by a series of observations over a period to observe directly whatever changes occur. All members of the present series of patients first became ill during the late summer of 1954. Members of the research team have now followed these patients for approximately eight months, and it is planned to continue the program of interviews, tests and observations throughout still another year, or until the patients have reached a fairly stable period of chronicity. A good deal of information of various kinds about these patients has been collected, by interviews with them at regularly scheduled intervals, by observation of them in the hospital and through the use of psychologic tests. Family members have been seen regularly in controlled interviews, and team members have talked at considerable length with various personnel of the treatment staff of the hospital about each patient. The research goal is not to study atypical behavior or to investigate psychiatric reactions as such, although deviant behavior is most carefully observed when it does occur. As an example, 1 young patient was followed through an acute reactive depressive episode lasting for two months, early in his convalescent stage. By and large, however, it is believed that this series represents a fairly typical or random sampling of patients and their families.

In terms of design and research goals, the study is still in its middle stages. At this writing most of the patients are midway in the experience of illness; all but a few have been discharged or are about to be discharged from the convalescent hospital, and many problems of orthopedic relevance are only now beginning to emerge. No summative statistical data and no final and decisive results are yet available. There has been sufficient progress, however, to warrant a brief report of some preliminary observations, to offer some illustrative material and to suggest some general interpretations of the kinds of behavior seen in these patients and in persons in critical relation to them. In effect this is a study of the emotional changes that take place at the same time as, and are presumably associated with, the physical changes with which the orthopedic surgeon is familiar. In reporting these experiences and tentative results we understand clearly that the surgeon, standing in crucial and powerful association to the patient, will make the ultimate evaluation of the worth of such observations to problems of orthopedic treatment. In this undertaking it is hoped that the patient may make fuller use of his resources — and these resources certainly include what the physician has to offer him — in his rehabilitation.

In a preliminary analysis of the many observations so far made, some fairly consistent patterns of behavior begin to emerge. What follows is a description of a few such clusters of observations, together with some indications of their possible relevance to the goal of total rehabilitation.

Multiple Etiologic Ideas

Almost all the patients and the families in this study have expressed an extraordinary range of etiologic notions about the disease, and this despite the wide dissemination of medical information about poliomyelitis in the public press and through other communication mediums. In the past few years it is difficult to see how the average person could escape the wide impact of publicity and propaganda about poliomyelitis; yet it appears that much of the folk-

lore about the disease shows remarkable resistance to extinction. The vigor and durability of these magical beliefs should not be passed over lightly, because the unreal and medically distorted etiologic ideas of the family are potent determinants of the fixed attitudes that exist in the mind of the patient and that, in one way or another, he brings to bear upon his treatment. Typically, patients hold a varied assortment of etiologic notions, some reasonable and some bizarre. For example, a six-year-old girl with a severe involvement of one leg and a minimal involvement of the other expressed at least eight distinct theories about the cause of her disease. At one time she suggested that she might have "caught it from a neighbor." At other times she variously attributed significance to being lazy, to getting tired, to riding her bicycle, to an injection received in school and to having been "beaten up" while walking home from school. On one occasion she expressed the idea that she had been poisoned by her teacher. The conception that this young patient has elaborated at greatest length has a kind of gastrointestinal orientation, and is in her mind somehow related to the fluid diet instituted in the acute hospital. This child believes strongly that poliomyelitis is basically a kind of stomach upset.

Shortly before this patient was discharged from the acute hospital, her mother told a research investigator of her conviction that the poliomyelitis had been caused by water bugs in the basement of the home. The family dog had eaten the bugs, and then licked the face of the patient. This was the mother's theory of causation. The father had entirely different ideas. In an interview some weeks later, he developed at length a theory that their child's infection had been caused by the pollution of air because of the plowing of a field nearby. He had observed that the incidence of poliomyelitis in the city seemed to be highest in areas where new housing developments were being constructed, and had concluded that clearing land, digging foundations and the like were connected in some way with the spread of the disease.

Much compressed, this is a sample — by no means atypical — of the range of multiple etiologic explanations expressed by the children and parents in this study. In similar fashion other patients and their families have presented a variety of causative ideas extending from the rational to the irrational and from logical to absurd. That these ideas exist at all is of more than passing interest; that they persist during the course of the patient's treatment, and after the parents have conferred with medical personnel about the patient's disease, is of indisputable significance. For these notions, often bizarre, medically faulty, but strongly held, must make some contribution to the attitudes about treatment methods that are held by the patient and the members of his family.

Reaction to Immobilization

Motility and Guilt

Interviews with various hospital personnel about these patients and direct observation in the hospital suggest that as a group they may be described as "good patients." These children accept hospital routine well; they seem to adapt easily to the regimen of treatment and accept immobilization and other forms of restraint and inactivation with a certain contentment and submission. Children who are rebellious or resistant to restraint are rare; these patients conform, or seem to conform, to a very constricting and controlling kind of environment. Nurses have commented that these children "never say a word about being on a frame," and "never even ask for a pillow." Often, the attitude of submission appears to be much more than that of passive compliance. After being returned from physical therapy, a child who "never complained" about a frame called the nurse's attention to some loose straps that she had neglected to tighten.

In studying hospitalized children, other investigators have noted with interest this general reaction to immobilization of "contentment" and "happy submission," both in orthopedic[3] and general-hospital[4] settings. This acceptance of motor restraint is to a degree unaccountable; it is a somewhat unexpected reaction. When one speculates about the determinants of this behavior, a cue of seeming significance is the observation that, in talking freely about poliomyelitis, these patients tend selectively to focus upon movement and motility.

Motility is surely a core factor in the life and development of the child. Of itself a primary urge or drive, motility is intimately connected with nearly all his physiologic and psychologic functions. Physiologically, it is associated with basic oral, excretory and genital functions; it is critically related to such matters as self-preservation. Psychologically, it is an all-important means of reality testing, integration, self-assertion and independence. Motility finds a multitude of functions: it may be a basis for anxiety[5]; it may be a means of expressing aggression[6]; it may of itself give pleasure.[7] In its diversity of interrelations with other functions motility may have many meanings for a child that are symbolic of more than simple motor action. The young child who learns to refrain from crossing the street by himself because of his parents' repeated injunctions that this behavior is dangerous is in effect learning to inhibit a symbolic kind of self-assertion. The child who is punished when he kicks other people may learn to control this symbolic expression of aggression. Such kinds of motor behavior are certainly weighed heavily with symbolic content. The independent and self-assertive child who wants to cross the street by himself, or the aggressive youngster who has the impulse to kick

people, must restrict his motility to avoid either punishment or pangs of conscience for doing something he knows is disapproved.

Among the patients in this study, motility seems to be an axis around which most conversation about poliomyelitis revolves. The children tend to connect the onset of the disease with motor activity, and in the context of a particular and characteristic emotional reaction. This is best described as a pervasive feeling of guilt. Guilt as a reaction to illness has been observed in other studies of poliomyelitis[8]; it has also been noted in connection with such pathologic conditions as fractures,[9] cancer[10] and nonspecific respiratory infections in children.[11] In the present study it is as if the patient thinks in such direct and elemental terms as these: a terrible thing has happened to me — I must have done something terrible to make it happen. Clearly suggested here is the primitive law of the talion: the very organ that has sinned must be punished.[12] To the child the "sin" has been performed by his legs, and retaliation has taken the form of the paralysis of his legs. Thus, the emotional reaction is readily attached to motility, especially physical activity that is not approved by the parents.

The feelings of guilt that harass these children often find simple and direct expression. One young patient said that he got poliomyelitis because he ran around and played too much. An adolescent girl attributed her infection to having played on a trapeze in the cellar of her home during her mother's absence; it was established that this was the first time she had played in the basement since the maternal grandfather had committed suicide by hanging, on the same trapeze, some months earlier. A six-year-old boy remarked that he "wore his legs out" by running around or riding his bicycle. An eleven-year-old convalescent patient stated that if he is cured he is going to stay home with his mother, his father and his younger brother. "I won't feel like running around any more then."

Guilt feelings, and fear of further punishment, in some cases are projected forward in time, and may be recognized as controlling determinants of future activity. After discharge from the convalescent hospital, one six-year-old girl commented that she would have to return to the hospital if she became tired from walking or riding her bicycle. "I would have the same thing I had before."

These, by illustration, are sentiments that were frequently expressed by patients in the study; to some degree they may account for the ease with which the children accept immobilization and hospital routine. It appears, in a word, that this behavior may be related to the guilt they feel for having done something that made them sick. Their compliance and conformity with immobilization seem to be much akin to atonement for guilt.

Problems and Parental Influences after Discharge

The material so far collected strongly suggests that the problems that poliomyelitis poses for the patient and his family, whether they are neurologic, orthopedic, social or emotional, do not often come into clear focus until the patient leaves the convalescent hospital. Opportunities for widely variant behavior are minimized in the controlled environment and standardized treatment situation of the hospital; if adjustment difficulties occur, they are seen most clearly when the patient re-establishes his relations to family members and when the family is adapting itself to the new situation at home. Emotional undercurrents, which sometimes may only be guessed at during the period of hospitalization, come to full flower when the patient is no longer under the direct influence of treatment personnel. As an example, a six-year-old girl placidly and proudly accepted a lower-leg brace at the convalescent hospital, learned to walk with a crutch and was discharged; shortly after she returned home, she told her mother she wanted to burn the crutch and then used it to attack her younger sister.

Other investigators have expressed the conviction that the role of the family is all-important in the patient's adjustment to a treatment situation.[8] In large measure this observation is supported by the data being collected in the present study. Both observational and interview material indicates, however, that parental influence should be appraised from the time of discharge from the convalescent hospital. During the period of hospitalization the patient's life space is overspread with treatment procedures, relations with professional personnel and other patients and the over-all impact of his new environment, and accordingly the parental role is somewhat de-emphasized. After discharge, parental influence in determining the course of the patient's progress is quickly re-emphasized. The attitudes of parents are seen as important predictive keys to the course of rehabilitation, in some cases so potent as to appear independent of other determinants.

For example, 2 patients with poliomyelitis were recently discharged from an orthopedic hospital, a six-year-old girl with a relatively severe leg residual, and an eleven-year-old boy whose involvement was considerably less marked. Both children had convalesced well, and both had been fitted with braces before they left the hospital. Within a week of discharge, each child was seen by a member of the research staff, and another team member interviewed the mother. The six-year-old girl, with the greater residua, had already returned to school. She washed and dressed herself, put on her brace with no assistance from her parents, and was vigorously expressing her independence in other ways. The overprotective parents of the older boy, on the other hand, insisted

on helping him with his brace; he was being bathed and dressed by his mother, who had also refused to allow him to return to school. It is anticipated that these 2 children will show entirely different patterns of behavior as time goes on, and one might equally speculate whether the behavior and attitudes of the parents will be significant in such differences as do occur.

The effect of attitudes of parents on the psychologic adjustment of the patient may be observed most clearly when the parents' attitudes are reinforced or brought into sharper focus by the pathologic process. In adjustment to the convalescence of a sick child, and in appraising his future development, the parent — either knowingly or unknowingly — may exploit situational factors in the illness to strengthen his own attitudes toward the patient. The disease or its sequelae become in effect a tool used to direct, to influence or to control. The parents of a thirteen-year-old girl were interviewed at length during her hospital convalescence. The father was a quiet, inconspicuous, inarticulate person of limited education, who worked as a truck driver. The mother, a briskly energetic, highly vocal little woman, was a schoolteacher, and impressed the observer as a strongly dominant person. In talking about the patient, who had a considerable bilateral paralysis of the lower extremities, the mother centered almost exclusively on the scholastic performances of the girl, the family's ambitions for her to become a schoolteacher and its gratification over her superior school work. The parents assessed the disability primarily in terms of its possible effect on the patient's academic training; other considerations were involved, but remarkably little importance was attached to them. Before the onset of the disease the patient had been allowed to participate only minimally in the social activities of her age group; her recreation was reading, she applied herself devotedly to her studies and seemingly had incorporated her mother's ambitions for her. After her discharge, this pattern was re-established with even greater intensity than before. The patient returned to school, was given tutorial assistance to make up the work she had missed and, because of her disability, was allowed no other activity. In this case the mother clearly was employing the situation of illness to fortify the values she held for the patient, and she conceived of rehabilitation entirely in these terms.

Doctor-Patient Relations

At this writing interviews with patients and their parents have accumulated to more than twenty hours for each case, and it was expected that these interviews would yield fruitful material about the doctor-patient relation in the hospital during the acute and convalescent periods. Analysis of the verbatim transcripts of these interviews reveals, surprisingly, that only a few of the informants have anything to say about the doctor, and that these few say very little. The average patient does not seem to see his doctor very often, and the doctor does not make much impression on him. The physician is typically seen in the role of a somewhat remote gatekeeper — the person who decides when the patient can go home. As perceived by the patient the role of the physician here appears to be quite different from that in some other medical situations, in which the patient identifies himself closely with his doctor, whom he views as playing the central therapeutic part in the experience of the illness.[10]

When the patient sees the doctor as participating but marginally in his treatment, he attaches greater significance to other people in the hospital environment. In this series the physician's role is definitely eclipsed by that of the physiotherapist. Without exception these children have talked freely and at length about the physiotherapist, and with a good deal of emotional involvement. Of the hospital personnel, the patient knows the physiotherapist best of all; he believes that the physiotherapist's activities are most central to his progress, and he forms a strong positive attachment to him. In short, the patient places the physiotherapist in stage center of the treatment process.

The decreased role of the physician in the eyes of the child may stem realistically from the fact that physical therapy is carried on daily whereas the doctor's visits occur much less frequently. In his professional role the physical therapist manipulates the patient's muscles and body, applies massage and very intimately directs movements during exercises. Procedures of this kind can contribute heavily to the therapist-patient relation.[13] The physician's relation to the patient, on the other hand, is much less intimate and involves less physical contact. It appears, too, that in terms of treatment goals the patient distinguishes the physician from the physiotherapist in a way facilitating a greater identification with the latter. Informants have repeatedly stated that the physician is primarily concerned with long-range goals and with comprehensive and rather gross aspects of progress. In a different way the physical therapist, with the patient, is responsive to the barely perceptible change — today's flicker of muscle action where none could be found yesterday, the smallest index of day-to-day gain, which receives the concentrated attention of both participants. The close relation between physiotherapist and patient is built in considerable measure on the shared experience of these small increments of muscle action.

The patients in this study continue to think of the physician as an important and influential figure, who can prescribe braces or discharge the patient from the hospital. But the doctor is at a distance, a lesser part of the experience of illness, and the patients tend to interpret and to ascribe motives to his with-

drawal. Some of these patients have been clearly observed to be becoming convinced that they have been rejected by the physician. "I never see him very much." "The last time I saw the doctor, really, when he came to see me, is when I got my brace. He asked me how I was and looked at the brace and then he left." "He is very busy and he doesn't come here very much." To a degree some of the same feeling is described by parents, who may say that consultations with the doctor are difficult to arrange, and who often remark with resignation — and rationalization — that their child's case is not as critical as some others.

Rejection by the physician or not, it is often so perceived. And a practical result of this perception is that the patient and members of his family cannot take full advantage of the wisdom and advice that the physician has to offer. This in some measure may account for the curious misconceptions and strangely distorted medical knowledge held by patients and parents alike. It suggests, too, the possibility of a barrier in the relation between doctor and patient after discharge — a handicap to management problems in the later convalescent and rehabilitative periods.

Summary

This is a selective and preliminary report of an investigation of a series of children with spinal poliomyelitis, all with some degree of lower-extremity involvement. The purpose of the study is to examine adjustment processes in the total experience of the disease by controlled observations of the patient and the persons in significant positions of influence to him. It is believed that this study will yield findings directly relevant to the broader field of physical disability. The interdisciplinary research team has used the technics of psychiatry, psychology, sociology and pediatrics to follow these cases for approximately eight months after onset. A partial analysis of the data collected to this point indicates that the typical patient and his family present multiple and medically distorted etiologic ideas, strongly held. Communication with medical and hospital personnel during the experience of illness, as well as information supplied to the patient and his family in these relations, has not extinguished these beliefs, which are obstructive factors in treatment and rehabilitation. The unqualified acceptance by these patients of immobilization procedures and their high conformity to hospital routine have been related to an emotional reaction of guilt, especially in the context of restricted motility. For many of these patients compliance is equated with atonement for their feelings of guilt. Both interview material and direct observation indicate that in the hospital parental influence on the adjustment of patients is sharply de-emphasized. After discharge, parental attitudes appear to be salient, predictive determinants of the course of rehabilitation. In this study the role of the doctor is seen to be less influential than that of other treatment personnel: the average patient has not identified himself closely with his physician. Patients and members of their families have interpreted the behavior of the physician in the convalescent hospital in terms of withdrawal and rejection.

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CORROSIVE (ACID) GASTRITIS*

Management of Early and Late Cases

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THE American literature contains comparatively few reports of cases of corrosive gastritis, of either the acute or the chronic variety. Because few patients survive the initial insult for more than twenty-four hours, the concept of the management of such cases is somewhat nebulous. Some of the reports in the literature deal primarily with the late sequelae of corrosive poisoning. Very few patients have survived the initial insult long enough to be followed under medical supervision until the late sequelae of pyloric obstruction appeared. Some steps in the management of such cases have been referred to in a previous publication by one of us (F.S.) and will be reiterated subsequently.

The 4 cases of corrosive poisoning reported below (1 after operation) clearly illustrate the steps in adequate and inadequate management.

CASE REPORTS

CASE 1. M.D., a 36-year-old woman, entered Cook County Hospital on December 8, 1953, because of hematemesis.

Eleven days previously, just after her Thanksgiving dinner, she had become depressed because of her husband's desertion, and she had ingested 59 ml. (2 ounces) of a material that she thought was "lye." (It was later established that she had ingested "Snobol," a commercial disinfectant containing hydrochloric acid.) She immediately fainted and fell to the floor. Her relatives found her lying on the floor, rushed her to a hospital, where her stomach was "pumped." She was released from the hospital the next day, at her own request, despite the fact that she remained very depressed, complained of burning of her throat and stomach and vomited both liquid and solid food. At home she continued drinking beer excessively despite her symptoms. On the day before admission she drank very heavily and this was followed by emesis of about 1 liter of bright-red blood. On the day of admission she vomited another 500 ml. of blood and was therefore admitted as an emergency to Cook County Hospital.

Physical examination revealed a well developed and well nourished, pale woman complaining of substernal pain. Examination of the oropharynx was negative. The lungs were clear to percussion and auscultation; the heart was of normal size and configuration, with rapid heart tones but without murmurs or other abnormal sounds. The abdomen was soft and nontender, and no masses were palpable.

The temperature was 99°F. by mouth, the pulse 132, and the respirations 26. The blood pressure was 82/68.

The examining physician made a diagnosis of corrosive esophagitis due to lye ingestion, with esophageal varices and other causes of massive upper gastrointestinal hemorrhage to be considered.

The patient was treated with whole-blood transfusions, infusions of 5 per cent dextrose in physiologic saline solution, antibiotics and milk and olive oil alternately by mouth. Phenobarbital and atropine were given by hypodermic injection. She improved rapidly and was subsequently placed on a bland diet, which she tolerated quite well. On the 6th hospital day a fluoroscopic examination with Lipiodol and then barium revealed a normal esophagus. Accordingly, she was discharged on the 7th day to the gastrointestinal outpatient clinic on a bland diet and antispasmodics.

She was next seen 3 weeks later by the clinic physician with complaints of a weight loss of 13.6 kg. (30 pounds), weakness and inability to keep solid or liquid food in her stomach. She stated that she vomited either immediately or 2 or 3 hours after eating. Because of these symptoms she was readmitted to the hospital.

Physical examination revealed an alert, co-operative woman, with evidence of weight loss. Examination of the head, chest and abdomen was negative. The physician's impression was esophageal stricture secondary to lye ingestion, with esophageal varices, diaphragmatic hernia, alcoholic gastritis, peptic ulcer and hysteria to be considered.

The pulse was 72 and regular, and the respirations 18. The blood pressure was 114/70.

Urinalysis was negative for sugar, albumin, acetone, urobilinogen and bile. The blood Kahn test was negative. Examination of the blood showed a red-cell count of 4,200,000 with a hemoglobin of 80 per cent (Sahli), and a white-cell count of 6200, with a normal differential. The nonprotein nitrogen was 30 mg., the total protein 7.4 gm., the thymol turbidity 6 units, the gamma globulin 1.45 gm. per cent, and the total cholesterol 184 mg. per 100 ml., and the alkaline phosphatase 3 Bodansky units. Cephalin flocculation was negative. A bromsulfalein test revealed 2.8 per cent retention of the dye after 30 minutes. The patient was given a semisolid diet, sedation and antispasmodics but continued to vomit periodically, usually an hour or so after meals, stating that milk "curdled" in her stomach and caused the emesis. She remained weak and depressed. The abdomen was always scaphoid and nontender. Because of the persistent vomiting she was placed on a liquid diet, with antispasmodics by hypodermic injection. Only minimal improvement was noted on this regimen. Since the ward physicians had never witnessed any vomiting episodes, they thought that they were dealing with a reactive-depressive neurosis. On the 11th hospital day a barium-meal examination of the stomach disclosed a normal esophagus, slight irregularity of the cardia of the stomach, with admixture of retained food material, and an area of constriction in the antrum, with marked distortion of the mucosal pattern (Fig. 1). The 6-hour film revealed some distribution of the barium throughout the small bowel, most of the barium remaining in the stomach (Fig. 2). The diagnosis was corrosive pyloric stenosis.

The patient was transferred to a surgical service, where she continued to vomit intermittently. There was no free acid in the gastric juice even on histamine stimulation. On February 5, 1954, exploration under general anesthesia revealed a thickened stomach wall with stenosis of the distal 8 cm. of the pyloric antrum. The duodenal bulb was normal. A retrocolic gastrojejunostomy was performed with the posterior wall of the antrum proximal to the stenosis anastomosed to the jejunum. The postoperative course was uneventful, and she was discharged to the outpatient clinic on February 12.

When seen in March in the gastrointestinal outpatient clinic she felt fairly well and had gained 1.8 kg. (4 pounds). She stated that emesis was occasionally present after heavy foods. She still felt weak and was slightly depressed. Her relatives reported that she was drinking excessively.

CASE 2. R.D., a 49-year-old man, was transferred to Cook County Hospital as an emergency on January 4, 1955, from

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a private hospital, where lavage with baking soda and milk had been carried out after ingestion of 80 to 120 ml. of a soldering acid 3 hours previously. On admission, he was retching and moaning with pain and frequently vomited small amounts of white, curded material. Because he was confused and apprehensive an adequate history was obtained with difficulty. He stated that his wife had died recently and that, feeling depressed and lonely, he had swallowed the soldering acid in an attempt to end his own life.

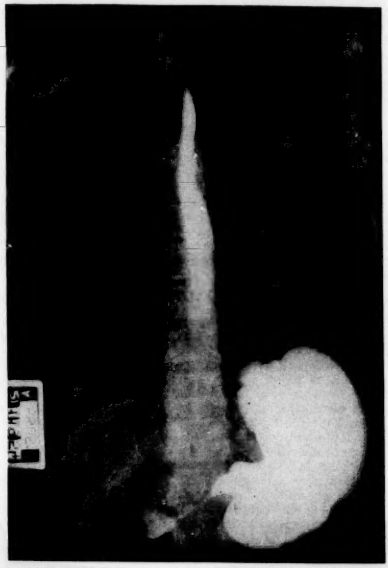

FIGURE 1. *Constricting Deformity of the Antral Portion of the Stomach in Case 1 Six Weeks after Ingestion of an Acid-Containing Disinfectant.*

Physical examination revealed a well developed man complaining of abdominal pain. Small, white, macular areas were scattered over a hyperemic buccal mucosa, tongue, epiglottis and oropharynx. The heart and lungs were within normal limits. The abdomen was scaphoid. Epigastric tenderness was elicited on deep palpation. No rebound tenderness or palpable masses were noted. The bowel sounds were normal. Rectal examination revealed a foul-smelling, grayish-brown stool with a positive benzidine reaction.

The temperature was 99°F. by mouth, the pulse 100 and regular, and the respirations 10. The blood pressure was 140/80.

Laboratory studies revealed a blood nonprotein nitrogen of 38 mg. per 100 ml.; the sodium was 131 milliequiv., the chloride 91 milliequiv. and the potassium 4.3 milliequiv. per liter, and the carbon dioxide combining power 56 vol. per cent. The hemoglobin was 95 per cent (Sahli), and the white-cell count 19,800, with 81 per cent neutrophils, 12 per cent band forms, 6 per cent monocytes and 1 per cent lymphocytes.

The diagnosis was acid burns of the oropharynx, esophagus and upper gastrointestinal tract. Treatment consisted of demulcents, antibiotics and a liquid diet.

On the next day the patient felt much better and was in no distress. On the 3d hospital day he became dyspneic and complained of severe epigastric pain. He did not vomit and could swallow fluids. The abdomen was distended and rigid. The bowel sounds were faint and infrequent, and marked tenderness, with rebound tenderness, was present over the entire abdomen. He was given fluids intravenously, and Wangensteen suction was started. A surgical consultation was requested. The surgical consultant thought that the patient had a ruptured viscus, and advised immediate exploratory laparotomy.

The patient was accordingly transferred to the surgical service, and a laparotomy was performed under general anesthesia on January 6, 61 hours after the acid ingestion; 100 ml. of turbid fluid was encountered in the peritoneal cavity. The distal third of the stomach was gray and necrotic appearing. A 50 per cent gastric resection with an antecolic gastroenterostomy was performed.

Pathological examination of the resected distal half of the stomach and 1 cm. of the duodenum revealed an injected serosa with fibrinous adhesions. The wall was diffusely thickened to 5 mm. The mucosa was pinkish green, with

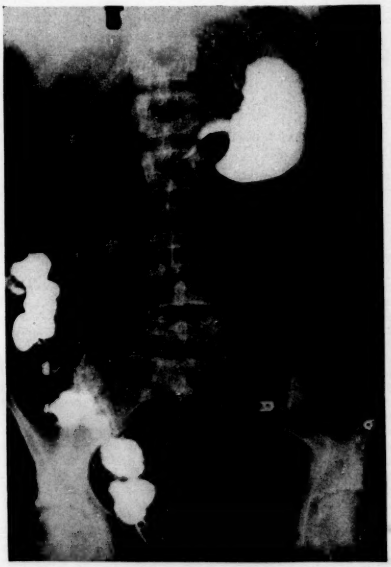

FIGURE 2. *Six-Hour Film in Case 1, Showing Persistence of the Constricting Deformity of the Antrum and Marked Retention of Barium in the Stomach.*
A small amount of barium is noted in the distal ileum and ascending colon.

numerous small erosions scattered over the surface. There was a cobblestone appearance to the intact mucosa (Fig. 3).

Microscopical examination of the stomach wall showed a severe acute gastritis with a marked inflammatory reaction in all layers of the wall and many zones of necrotic tissue.

The usual postoperative routine was followed. The patient was alert and co-operative for 3 hours after completion of the surgical procedures. On the 1st postoperative day he became anxious and tachypneic. Turbid, brown fluid with flecks of tissue was returned through the gastric suction tube. On the next day, the abdomen became distended, the temperature rose to 104°F. by mouth, and the dyspnea increased. Moist rales were heard over the right-lung field anteriorly and posteriorly. Because he was able to cough up

some purulent yellow sputum, bronchoscopic aspiration was not considered necessary. Penicillin and streptomycin were instituted in addition to oxytetracycline, which he had been receiving intravenously. In spite of carbon dioxide inhalation, alcohol and water sponges, he became cyanotic and died during the evening of the 2d postoperative day.

At autopsy the coroner's pathologist reported a gangrenous gastritis due to zinc chloride ingestion, focal fibrinous peritonitis and ileus, pneumonia of the right middle and upper lobes; acute esophagitis and tracheobronchitis; septic softening of the spleen; cloudy swelling of the myocardium and parenchymatous organs; and a recent gastric resection with acute duodenitis of the stump. The specimens of the stomach and jejunum revealed diffuse areas of gangrene involving almost the entire portion of the remaining stomach and the site of anastomosis with the jejunum (Fig. 4).

CASE 3. M.S., a seriously ill, 65-year-old man, was admitted to the medical service of Cook County Hospital on April 14, 1955. One hour previously he had attempted suicide by ingesting approximately 90 ml. of formaldehyde.

FIGURE 3. *Resected Specimen of the Stomach in Case 2, Showing Edema and the Marked Cobblestone Appearance of the Mucosa, with Numerous Small Erosions Scattered Throughout.*

Physical examination revealed a confused, elderly man in mild shock, complaining of severe generalized abdominal pains. The skin was cool and clammy. The abdomen was scaphoid; there was muscle guarding but no rebound tenderness. Bowel sounds were normal in character and frequency. No stool was obtained on rectal examination.

The pulse was 150 and regular but thready, and the respirations 36. The blood pressure was 100/70.

The diagnosis was corrosive gastritis due to formaldehyde.

Aspiration and washings of the stomach were initiated, with a return of approximately 100 ml. of foul-smelling, clear, yellow, benzidine-positive fluid. A urinary catheter was inserted, and 50 ml. of clear yellow urine with a specific gravity of 1.020 was obtained that was negative for albumin, sugar and acetone. Blood chemical examination revealed a sodium of 141 milliequiv., chloride of 96 milliequiv. and potassium of 4.9 milliequiv. per liter, with a carbon dioxide combining power of 48 vol. per cent. Examination of the blood showed a hemoglobin of 103 per cent (Sahli) and a white-cell count of 9100, with a normal differential. The blood Kahn test was negative, and an electrocardiogram was within normal limits.

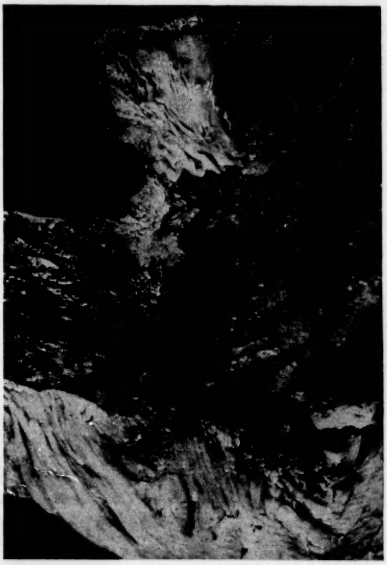

FIGURE 4. *Autopsy Specimen in Case 2, Showing the Diffuse Areas of Gangrene Involving the Remaining Portion of the Stomach and the Adjacent Jejunum.*

Intravenous infusion of fluids and antibiotics was started. During the 1st 12 hours, hourly blood-pressure determinations recorded a progressive fall, necessitating intravenous administration of nor-epinephrine solution. On the 2d hospital day the patient was mentally alert and able to take fluids by mouth. The urinary output, however, was only 90 ml. for the first 24 hours, gradually increasing to 1200 ml. on the 4th day. The nonprotein nitrogen rose from 57 to 142 mg. per 100 ml. during this time, with a creatinine of 4 mg. per 100 ml. Temporary clinical improvement was noted on the 3d hospital day. The nor-epinephrine was discontinued and the patient was permitted to walk. Two days later acute diarrhea developed, with 15 to 18 bowel movements a day, consisting of small semiformed benzidine-positive stools. This was associated with generalized abdominal tenderness and distention. Oral feedings were stopped, and intravenous therapy was again started. On the following morning, rebound tenderness was elicited, with absent bowel sounds. An emergency film of the abdomen with the patient upright showed free air under the right hemidiaphragm. A surgical consultant advised immediate exploratory laparotomy. At operation a chemical fixation of the stomach with pneumatosis of the greater and lesser omentum and a sealed-over perforation of the lesser curvature in the pars pylorus was found. Immediate closure without further manipulation was considered the procedure of choice, and the operation was terminated as an exploratory one. The postoperative course was characterized by spiking

temperatures, mental lethargy and Kussmaul breathing although the abdomen remained soft and scaphoid and the bowel sounds again became active. Moist rales developed in both lung bases, and the patient died on the 3d postoperative day.

CASE 4. W.L., a 63-year-old man, was admitted to Cook County Hospital on September 8, 1955, about 8 hours after drinking an undetermined quantity of soldering fluid — probably in a suicidal attempt because of depression. Shortly after he drank the soldering fluid he was taken to a hospital

FIGURE 5. *Constricting, Smooth Deformity of the Lower Half of the Stomach in Case 4 Approximately Two Weeks after Ingestion of Muriatic Acid.*

in his vicinity for 1st aid. He was given 2 glasses of egg white and mineral oil and then sent to Cook County Hospital.

Physical examination showed a well developed and well nourished man lying quietly in bed who did not seem to be in severe distress. No signs of burns around the mouth were noted. The lips were red; the tongue was heavily coated with whitish material. There was no bleeding from the mouth, and there was little edema of the oropharynx. He could swallow water and speak with some difficulty. The neck was normal, as was the chest and its contents. The abdomen was flat and soft, without palpable masses. The bowel sounds were active. No abdominal tenderness was noted. There were no significant findings on examination of the back or the extremities.

The pulse was 84 and regular, and the blood pressure 170/80.

A diagnosis of corrosive gastritis was made, and the patient was put on a suitable regimen of liquid diet with demulcents, antispasmodics, sedatives and antibiotics.

Despite the instituted treatment whitish, tender plaques developed in the mouth, with swelling of the palate, and he started to vomit intermittently. He ran a slight temperature and began to lose weight. After dilatation of the lower esophagus with a No. 38 bougie, he seemed to be able to eat slightly better.

Urinalysis was negative. The hemoglobin was 105 per cent (Sahli), and the white-cell count 19,900 with 74 per cent neutrophils and 18 per cent band forms. The blood Wassermann test was negative. The nonprotein nitrogen was 59 mg., the creatinine 2.4 mg., and the total protein 7.5 gm. per 100 ml.; the sodium was 128 milliequiv., the potassium 4.5 milliequiv., and the chloride 93 milliequiv. per liter.

A gall-bladder film was normal, and barium-enema study was negative. X-ray examination of the stomach showed a smooth narrowing of the distal half of the stomach highly suggestive of cancer even though a stricture that had followed a corrosive substance was not ruled out (Fig. 5). A second gastrointestinal series 3 weeks later showed a more marked narrowing of the antrum, which now had a spindle-shaped appearance (Fig. 6).

Three weeks after admission gastroscopy, limited to the upper third of the stomach, revealed a boggy, hyperemic mucosa that bled easily. Supportive treatment was continued, and preparations made for operation.

At laparotomy on November 10 the stomach was found to be small, shrunken and adherent to the posterior wall. Because it was thought that any surgical procedure on the stomach at this time would be against good surgical judgment a jejunostomy was done, and the abdomen was closed. The patient made an uneventful recovery and was discharged 4 weeks later on jejunostomy feedings. He is being prepared for later gastric surgery (gastroenterostomy).

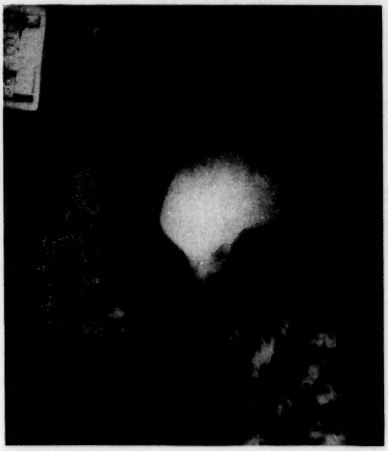

FIGURE 6. *Progressive Narrowing of the Lower Half of the Stomach, with Signs of Retention, Three Weeks after Figure 5 Was Taken.*

DISCUSSION

Corrosive gastritis results primarily from ingestion, either accidentally or with suicidal intent, of commercially available mineral acids such as hydrochloric, sulfuric, nitric and carbolic acids or corrosive alkalis. Alkalis exert their primary, destructive effect on the oral and esophageal mucosa, with only minimal involvement of the stomach, probably because of their neutralization by the highly acid gastric secretions. Contrariwise, acids, according to Boikan and Singer[1] and Meyer and Steigmann,[2] only sear the esophageal mucosa but flowing along the magenstrasse of the stomach, depending on the type and quantity of acid ingested, cause rapid coagulation necrosis of one or more layers of the stomach with the following se-

quelae: acute destruction of the gastric wall, with peritonitis; hemorrhage either immediately or in a few days to weeks; and destruction of the superficial layers, with edema and inflammation and loss of the gastric glands and intrinsic nerves and finally fibrosis with scarring.

The ingested agent flowing along the magenstrasse reaches the pyloric sphincter and antrum. Owing to the ensuing pylorospasm the acid remains at this site, where its most deleterious action takes place. More extensive involvement of the gastric mucosa will depend upon whether or not the corrosive poison followed the partaking of a meal. On the basis of pathological studies, Gradman, Gerber and Kaiser[3] state that the end result may be pyloric stenosis, antral stenosis, hour-glass deformity or linitis plastica.

The esophagus and stomach are severely injured by ingestion of a corrosive agent. If an alkaline corrosive (lye) is ingested, most of the damage occurs in the esophagus. If an acid corrosive is ingested the esophagus suffers less damage, most of the destruction occurring in the stomach. The damage to the stomach is definitely conditioned by the amount of gastric contents present in the stomach at the time the corrosive acid is ingested. From past experience with similar cases, we believe that it is possible to state from the x-ray appearance of a patient's stomach several weeks or months after ingestion of the acid whether or not the acid was taken on a full stomach. The patients who ingest the acid when their stomachs are full usually show a small pyloric narrowing, sometimes about 1 cm. wide, which could easily be diagnosed as annular carcinoma of the distal part of the antrum. They also present a huge, distended stomach. The patients who have ingested the acid on an empty stomach present a diffuse involvement of the lower half or two thirds of the stomach, only the upper, fundic portion remaining uninvolved, which may become quite distended compensatorily.

If the patient survives the first twenty-four hours and does not die from the immediate shock associated with the corrosive, widespread maceration and necrosis of the mucosa of the esophagus or stomach occur, as seen frequently by the coroner's pathologists. This may result in severe mediastinitis after lye poisoning, and gastritis with upper abdominal peritonitis after acid poisoning. During this stage (a week or longer) the patient is still in danger because the mediastinitis or gastritis and peritonitis may be so severe that the tissues cannot recover and the patient ultimately dies.

However, if the injury, as determined by the amount ingested and concentration of the corrosive substance, is not overwhelming, the patient usually responds to a careful supportive therapeutic regimen, which should consist of sedatives, antibiotics, blood transfusions, fluids, with attention to the electrolyte balance, antispasmodics and various demulcents given by mouth.

It is important to keep in mind not to use any large stomach tube for stomach lavage when the patient is first seen after the ingestion of a corrosive agent because such a tube may increase the damage to the gastric or esophageal wall. However, weak emetics may be used, or preferably only demulcents such as egg white, milk and olive oil. These dilute as much as possible any irritant that is still present. For some cases a specific antidote can be given — for example, weak alkali for acids, lemon juice for alkali, plain salt for silver nitrate, and alcoholic beverages for carbolic acid.

During the acute stage when the patient presents the symptoms of peritonitis with tender, rigid, painful abdomen the dangerous impulse to perform an emergency laparotomy must be resisted. The experienced surgeon as a rule does not intervene during this stage because there is no actual peritonitis such as that seen after perforation of a hollow viscus. The rigid and painful abdomen is due to an irritation of the peritoneum by a necrotic organ without actual perforation (diffuse peritonitis). In this type of peritonitis, which is similar to that seen in severe cases of typhoid fever, regional ileitis or ulcerative colitis without actual perforation of the bowel, no surgery is indicated.

Occasionally, an erroneous diagnosis of peritonitis from a ruptured viscus is made because there is no history of intake of a corrosive substance. If the surgeon opens such an abdomen and finds a highly inflamed, almost gangrenous organ he should not start any surgical procedures but should only do a jejunostomy and close the abdomen. The jejunostomy may be useful to keep up the nutrition of the patient.

If the damage is not too severe so that the patient survives the first few days, nature as a rule will take care of the burned organ, by causing a slowly developing demarcation between the corroded and unaffected parts of the stomach. The patient may thus remain asymptomatic for weeks or even months. Then, depending on the pathologic changes that have occurred, he will present himself to the physician with one or more of the following symptoms: weight loss, anorexia, nausea, bloating, eructation, epigastric fullness and vomiting, either persistent or intermittent. Physical examination may reveal inanition, emaciation, dehydration, visible peristaltic waves in the upper abdomen or other signs of partial or complete pyloric obstruction, and laboratory examination may indicate severe electrolyte disturbance.

The course and appearance of symptoms described above are well illustrated by Cases 1 and 4, which also demonstrate the value of withholding operation and giving supportive treatment in these cases. The surgical intervention about eight and ten weeks after ingestion of the strong corrosive acid had much happier results for these patients than the laparotomy and subsequent gastric resection had during the acute stage in Case 2 and the laparotomy alone in Case 3.

It is obviously much easier for the surgeon to perform a gastroenterostomy on a stomach in which definite demarcation has taken place between the healthy and destroyed part of the stomach than to work on a stomach whose walls are macerated and necrotic. We therefore believe that a history of ingestion of a corrosive substance is a definite contraindication to an early laparotomy.

In most cases the various corrosive substances seem to have a definite predilection for damaging a specific organ. Thus, esophageal damage usually follows lye, and gastric damage acid ingestion. One finds, however, occasional reports of esophageal stricture in association with pyloric stenosis from acid ingestion[4] and of the coexistence of pyloric and esophageal lesions from lye.[5] One of us (F.S.) observed the presence of a slight esophageal stricture in a patient who had a severe pyloric stenosis after taking hydrochloric acid.

In the differential diagnosis of pyloric stenosis, especially in younger patients, one must consider the possibility of sequelae of corrosive gastritis. A diagnosis of carcinoma is often made[6,7] if an adequate history is not obtained. The history may not be obtained either because patients will not give it, if the acid ingestion has been in a suicidal attempt, or because the patient may not associate his present symptom with an occurrence several weeks or months previously. On the other hand, occasionally, the physician may erroneously regard the presenting symptoms described above as signs of a depressive neurosis because he fails to associate the previous suicidal attempt with the present condition.

Summary and Conclusion

The entity of corrosive (acid) gastritis, with its sequelae of pyloric stenosis, has received little attention in the American literature. It is not common knowledge that caustic alkalis exert their liquefaction necrosis primarily on the oral and esophageal mucosa, with little if any effect — in most cases — on the gastric mucosa because of the neutralizing action of the stomach secretions. Acids, in contrast, are notorious for their coagulation necrosis of the gastric mucosa with acute and chronic sequelae. The acute symptom may include hemorrhage, shock and "perforation" with peritonitis. The late sequelae may be classified according to the amount of destruction and the resultant scar formation: pyloric stenosis, antral stenosis, hour-glass deformity or rarely total gastric scarring resulting in a linitis plastica. The obstructive symptoms can begin anywhere from a few weeks to years, with an average of four to six weeks, after the acute phase of corrosive poisoning has subsided. The treatment of the acute state is supportive — medical. The treatment of the sequelae is surgical — pyloroplasty or gastroenterostomy, depending on the pathology found at laparotomy. Subtotal gastric resection is rarely indicated.

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TREATMENT OF CHRONIC GRANULOCYTIC LEUKEMIA WITH 1,4-DIMETHANESULFONYLOXYBUTANE (MYLERAN)*

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MADISON, WISCONSIN

HADDOW and Timmis[1] observed that 1,4-dimethanesulfonyloxybutane§ inhibited the growth of certain transplanted animal tumors and lowered the neutrophil count of the animals receiving the compounds. The structural formula of the drug is as follows:

Galton[2] and Galton and Till[3] presented the most extensive reports of its uses in the treatment of chronic granulocytic leukemia. At least two reports[4,5] and two abstracts[6,7] describing its use have appeared in the American literature. The general opinion expressed in the above reports is that the compound is a relatively safe, usually effective palliative agent in chronic granulocytic leukemia. Substantiated claims for prolongation of life cannot be made at present,

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§Available as Myleran from Burroughs Wellcome and Company, Incorporated, Tuckahoe, New York.

and the drug should probably be considered as another member of the group of agents known to exert a favorable influence on the course of some patients with chronic granulocytic leukemia.

The purpose of this report is to record the results and impressions in the treatment of 19 patients with chronic granulocytic leukemia during the past four and a half years. We have also treated 4 adult patients with acute leukemia but have not observed beneficial results and will not discuss these patients further.

TABLE 1. *Results of Treatment.*

Case No.	Hospital No.	Sex	Age	Duration of Symptoms before Therapy with New Compound	Previous Therapy	Condition Immediately before Therapy with New Compound			Best Condition after Therapy			Duration of Remission
						Hemoglobin	Size of Spleen	Leukocyte Count	Hemoglobin	Size of Spleen	Leukocyte Count	
			yr.	*mo.*		*gm./100 ml.*	*cm.*	*x 10³*	*gm./100 ml.*	*cm.*	*x 10³*	*mo.*
1	297870	F	20	1	None	10.8 (Aug., 1954)	2	77	14.3 (June, 1955)	0	12	18*
2	295972	M	67	1	None	10.7 (May, 1954)	0	293	12.1 (Aug., 1955)	0	89	17§
3	291212	M	40	1	None	12.0 (Sept., 1953)	3	160	15.3 (May, 1954)	0	9	30*
4	293823	M	57	2	None	11.1 (Jan., 1954)	13	568	13.4 (Sept., 1954)	4	12	10†
5	301808	M	52	4	None	10.7 (Apr., 1955)	14	269	14.3 (Sept., 1955)	5	16	6
6	301349	F	47	3	None	9.7 (Mar., 1955)	14	295	12.3 (Sept., 1955)	11	24	12*
7	264677	M	49	12	None	14.9 (July, 1955)	1	43	17.5 (Feb., 1956)	0	24	7*
8	172498	F	44	28	P^{32} (June, 1953)	10.6 (Sept., 1953)	1	85	13.9 (Dec., 1953)	0	13	14‡
9	253440	F	64	57	X-ray (Nov., 1951)	11.3 (Feb., 1952) 9.8 (Nov., 1952) 12.2 (Sept., 1953)	9 11 10	130 155 97	14.2 (June, 1952) 13.9 (May, 1953) 13.1 (Feb., 1954)	4 0 6	58 19 8	4 8 8†
10	301940	F	37	24	None	6.1 (Apr., 1955)	14	76	13.5 (Apr., 1956)	6	28	12*
11	296479	F	62	12	None	11.0 (June, 1954)	10 (?)	577	14.1 (Oct., 1954)	16	117	4§
12	289400	F	59	8	X-ray (May, 1953)	10.9 (Aug., 1953)	12	187	13.7 (Apr., 1954)	9	52	8‡
13	261367	F	62	36	Urethane (May, 1951); x-ray (July, 1951).	8.6 (Nov., 1951)	17	257	10.5 (Dec., 1951)	15	34	1‡
14	VA 115	M	—	53	X-ray (Aug., 1951)	10.5 (Mar., 1952)	15	322	10.3 (June, 1952)	15	10	3¶

*Remission continuing.
†Death due to other neoplasm.
‡Death due to leukemia.
§Then x-ray treatment to spleen because of persistent splenomegaly.
¶Death due to non-neoplastic disease.

Method and Dosage Schedules

Nineteen adults with chronic granulocytic leukemia were given the drug¶ daily by mouth in varying dosage. Previous treatment with other modes of therapy is indicated in Table 1, as is the total estimated duration of the disease. Nine patients had received no previous therapy. To estimate the duration of illness, the onset of the disease is considered as the time when the patient first noted symptoms that could fairly be attributed to this form of leukemia. Clinical remission was judged on the basis of subjective improvement, rise in hemoglobin, gain in weight, decrease in the size of the spleen and fall in leukocyte count. Leukocyte counts were obtained at intervals of one to four weeks, the longer intervals being in patients who were on maintenance therapy.

When this compound was first obtained, the initial dosage schedule was 25 mg. daily for six days. Cases 9 and 14 were thus treated, and precipitous falls in the leukocyte counts but no recognizable deleterious effects were noted. In most of the cases reported below, the initial daily dose was 4 or 6 mg. continued until the hemoglobin rose to normal or nearly normal. An attempt was not made to reduce the leukocyte level to normal though this was sometimes achieved before the hemoglobin reached a normal level. Therapy was temporarily discontinued when the leukocyte count fell below 10,000. The daily maintenance dose has been 1 to 4 mg. It is our current practice to use maintenance therapy. This practice is not based on any scientific data that we have gathered, and we can make no claim that maintenance therapy is better than interrupted treatment. Our belief is that if maintenance treatment is elected the dosage should be very conservative — that is,

¶The early supply of Myleran was kindly funished by Mr. G. Timmis and Dr. D. Galton, Royal Cancer Hospital, London.

not more than 1 or 2 mg. a day until it is evident that more is needed to maintain control.

Ten patients (Cases 1-10) enjoyed excellent remissions, and 4 (Cases 11-14) had fair to good remissions after therapy. Data on these 14 patients are presented in Table 1. Five of the 19 patients (Cases 15-19), as discussed below, derived no discernible benefit from the therapy.

TABLE 2. *Data in Case 9.**

DATE†	WHITE-CELL COUNT	HEMOGLOBIN	SIZE OF SPLEEN	THERAPY
	x 10³	*gm./100 ml.*	*cm.*	
5/5/47	341	10.0	11	X-ray
8/20	36	14.0	4	
10/11/51	244	12.5	8	X-ray
11/29/51	85	12.6		X-ray
2/21/52	130	11.3	9	1,4-dimethanesulfonyloxybutane (25 mg./day for 6 days)
3/6	87	12.0		None
4/17	23	12.6	7	None
5/15	38	12.5	2	None
6/26	58	14.2	4	1,4-dimethanesulfonyloxybutane (12 mg./day for 3 days)
8/21‡	103	TSF(8)		None
11/20	155	9.8	11	1,4-dimethanesulfonyloxybutane (25 mg./day for 4 days)
12/3	43	10.7		1,4-dimethanesulfonyloxybutane (2 mg./day for 8 days)
3/5/53	19	13.9		None
5/7	11	13.3	0	None
9/17	97	12.2	10	1,4-dimethanesulfonyloxybutane (2 mg./day)
10/8	65	11.0	11	1,4-dimethanesulfonyloxybutane (12 mg./wk. for 4 wk.)
11/5	38	11.8	9	1,4-dimethanesulfonyloxybutane (12 mg./wk. for 4 wk.)
12/17	12	14.3	6	1,4-dimethanesulfonyloxybutane (8 mg./wk.)
1/1/54	11	—	—	—
2/11	8	13.1	6	1,4-dimethanesulfonyloxybutane (4 mg./wk.)

*Patient died at home in June, 1954; bronchogenic carcinoma diagnosed by Papanicolaou-technic study of sputum and finding of carcinoma cells in bone-marrow biopsy in February, 1954.

†3 separate remissions bracketed.

‡Patient admitted to surgical service for correction of strangulated femoral hernia.

DISCUSSION

The response of some patients with chronic granulocytic leukemia to treatment with 1,4-dimethanesulfonyloxybutane is most gratifying. In addition to the objective changes listed in Tables 1, 2 and 3, the patients experienced a pronounced increase in feeling of well-being. Sweating decreased, and strength increased.

It is our impression that the most impressive responses occur in patients with recently diagnosed, typical disease not previously treated (Table 1, Cases 1-7). However, excellent improvement followed therapy with the new compound in several patients who had had the disease for several years and had previously been treated with radiation therapy (Cases 8 and 9, Table 1). For example, Case 8 died during an acute myeloblastic, thrombocytopenic episode after an eighteen-month remission. Case 9 died with bronchogenic carcinoma after thirteen months of intermittent therapy with the new drug preceded by intermittent x-ray therapy to the spleen; it was believed that she was unresponsive to x-ray therapy at the time of institution of treatment with 1,4-dimethanesulfonyloxybutane. She had three remissions, with a total duration of twenty months, after separate courses of therapy with the drug. One of the patients treated by Petrakis et al.[4] also died of bronchogenic carcinoma. Case 4 died of a glioblastoma multiforme after nine months of therapy. The leukemia appeared to be in an excellent remission up to the time of death, with a hemoglobin of 13.4 gm. per 100 ml. and a leukocyte count of 40,000. An extended period of observation of a large number of patients will be required to decide if the compound is a carcinogen as well as an antileukemic agent in human beings.

TABLE 3. *Data in Case 3 (No Previous Treatment).*

DATE	WHITE-CELL COUNT	HEMOGLOBIN	SIZE OF SPLEEN	DOSAGE OF 1,4-DIMETHANESULFONYLOXYBUTANE
	x 10³	*gm./100 ml.*	*cm.*	
9/22/53	160	12.0	3	25 mg./wk.
10/20	67			25 mg./wk.
11/10	37	13.3	4	25 mg./wk.
12/15	38	14.1		12 mg./wk.
2/9/54	18	14.1	0	12 mg./wk.
4/6	9	13.7	0	None
4/27	11			12 mg. once
5/18	9	15.3	0	None
6/8	14			12 mg. once
6/29	15	13.7	0	12 mg. once
9/13/54	9	13.4	0	None
12/6/54	27	14.8	2	12 mg. once
2/28/55	31	13.7		2 mg./day for 20 days
5/9	57	12.0	3	2 mg./day
6/27	37	11.5	3	2 mg./day
8/8	41	12.3	2	2 mg./day
12/12	20	13.2	0	2 mg./day
4/9/56	20	12.5	1	1 mg./day

In our opinion, the drug is definitely the best available to date and superior to urethane or Fowler's solution for chronic granulocytic leukemia. Our experience with radiophosphorus in the treatment of

chronic granulocytic leukemia is insufficient to allow us to compare it with the new agent.

Cases 15-19 were considered treatment failures. Case 15 (U.W.H. 36671), a forty-seven-year-old woman, had had chronic granulocytic leukemia for six years and was in the thrombocytopenic, myeloblastic stage of her disease when 1,4-dimethanesulfonyloxybutane, 25 mg. a day for six days, was administered. Within a month a severe hemolytic process was apparent, and she died two months after the start of therapy (total dose, 150 mg. in six days). Microscopical examination at autopsy showed a hypoplastic bone marrow. This is the only patient in whom significant marrow depression may have resulted from the therapy.

In Case 16 (U.W.H. 284915), a sixty-five-year-old man, symptoms of chronic granulocytic leukemia developed eight months before therapy was instituted. He had had no previous treatment. A surgical biopsy of the bone marrow showed a moderate degree of myelofibrosis, with leukemic marrow intervening. The new compound, 2 mg. daily, reduced the leukocyte count from 40,000 to 10,000 in a six-week period, but the hemoglobin did not rise and the spleen did not become smaller. Anemia became a severe problem, and the spleen grew larger. He died approximately eighteen months after the drug was first administered. X-ray therapy to the spleen in the interim had not been of benefit. He received at least 70 blood transfusions.

Case 17 (U.W.H. 265050) was a forty-eight-year-old man who had had typical polycythemia vera for five years before the picture of chronic granulocytic leukemia developed. 1,4-dimethanesulfonyloxybutane (70 mg. in twenty-eight days) was administered at a time when there was thrombocytopenia. The patient died with the clinical picture of cerebral hemorrhage.

Case 18 (U.W.H. 295437), a fifty-five-year-old man, had untreated chronic granulocytic leukemia estimated as of about thirteen months' duration. Treatment with 4 mg. of the new drug daily for sixty days resulted in a fall in the leukocyte count from 260,000 to 29,000, but there was no rise in hemoglobin and no subjective improvement. Subsequent x-ray therapy did not bring improvement, and the patient died in another city.

Case 19 (U.W.H. 218435), a sixty-five-year-old woman, did not have unequivocally diagnosed chronic granulocytic leukemia. The bone marrow was not diagnostic and she had leukopenia and thrombocytopenia when therapy was instituted. No benefit was noted, and the drug was discontinued after several months.

In summary of the 5 treatment failures, it should be noted that 2 of the patients had thrombocytopenia, and 1 had definite myelofibrosis, and in 1 the diagnosis was equivocal.

Purpura or other toxic manifestations described for this drug were not observed except possibly in Case 15. Administration of this compound caused no discomfort to the patients. Others[3,5] have noted bone-marrow depression that was probably due to this drug, and we believe it should be used only with genuine appreciation of its potential toxicity.

Summary and Conclusions

1,4-dimethanesulfonyloxybutane (Myleran) was administered orally for the treatment of 19 patients with chronic granulocytic leukemia. Good remissions lasting for one to thirty months were noted in 14 patients. Some of the remissions continue. Best results appeared in patients with recently diagnosed typical chronic granulocytic leukemia. Three separate remissions were induced by intermittent therapy in 1 patient. Remissions were characterized by a rise in hemoglobin, decrease in size of the spleen, fall in leukocytes and a prominent subjective improvement.

This drug is considered a very useful agent for the treatment of chronic granulocytic leukemia, and we are selecting it as the treatment of choice in some patients with recently diagnosed disease and in patients who no longer are controlled by radiation therapy.

We are indebted to Miss Frances K. Morris for technical assistance.

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MEDICAL PROGRESS

REGIONAL ENTERITIS*

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IN the early 1930's, two events provided a much needed stimulus for an awakened interest in the small intestine, that most neglected portion of the digestive tract whose importance in the body economy was in inverse proportion to knowledge of its physiology and function.

The development of a technic for rapid intubation of the gut has permitted studies on its secretory, motor and absorptive functions and led to procedures of great practical value in the management of patients with disorders of the small intestine.

Similarly, in separating from the heterogeneous group of benign granulomas of the gastrointestinal tract, a clinical and pathological entity now most often referred to as regional enteritis, Crohn et al.[1] have called attention to "one of the most puzzling and difficult fields of abdominal disease—the diagnosis of small intestinal lesions."[2]

In the ensuing years, since their first publication in 1932, much has been written about terminology, etiology, pathology and treatment, resulting in some revision and expansion of the original concepts, but the fundamental clinical picture and course have undergone very little modification. This report is intended as a brief review of the progress made in the understanding of regional enteritis and the reflection of such progress in the management of patients with this disease.

It in no way detracts from their contribution that one can cull from the earlier literature isolated and fragmentary reports of cases resembling regional enteritis.[3] Nonspecific granulomas involving segments of the entire alimentary canal, though mainly in the colon, had for many years been observed in relation to penetrating foreign bodies, trauma, herniation and vascular disturbances. It is from this large, motley group that a distinct entity was segregated with a characteristic clinical picture and, in the first group studied, anatomically limited to the terminal ileum and responding well to resection of the involved area.

Although the terminal ileum remains the most frequent site of involvement, the present pathological concept embraces the entire gastrointestinal tract from stomach to colon. The rapid changes in terminology from terminal to regional ileitis were dictated by a recognition of a more widespread distribution, as well as the dire prognostic significance of the original name. When in 1933-34 a similar picture was described in the jejunum, the term regional enteritis was suggested to include the entire intestinal tract.[4,5] The clinical picture has been so fully described that only the aspects attributable to involvement of the jejunum and duodenum will be alluded to here. Where there have been significant variations from the original thesis in recurrences, prognosis and therapy, these will be noted in an effort to formulate the present concept of this disease.

It is difficult to see how a condition as common as regional enteritis could have been present to the same extent before 1932 and escaped detection clinically, at operation or at autopsy. To be sure, many cases masqueraded as hyperplastic tuberculosis, inoperable cancer, mesenteric adenitis or acute appendicitis. Yet Crohn,[6] and Jeffrey[7] in Wilkie's clinic, even in retrospect could not find from their own surgical or post-mortem files accumulated before 1930 any significant amount of what is now recognized as regional enteritis. Even considering that reference to any new clinical entity is soon followed by reports of its increasing frequency, the disparity in incidence before and after 1932 is unusually great for this condition. The absence of autopsy confirmation is partially explainable by the fact that patients with regional enteritis rarely die of this disease, unless they have had earlier surgery. If this represents a true increase, the nature of the responsible circumstances — dietary, bacteriologic or environmental — cannot be elicited at present, except for the thesis that one is dealing with the sequel to an increasing prevalence of infection with bacillary dysentery.

Though the exact incidence of this disease is unknown — estimated at a fifth of cases of ulcerative colitis as seen in the hospital population — it is sufficiently common and of such protean manifestations as to make it an important diagnostic possibility. One has only to list the symptoms and findings, including the possible complications, to realize the wide range of its medical and surgical aspects.

As with the history of the development of intestinal intubation, in which there was in one institution — the Hospital of the University of Pennsylvania — a confluence of individuals ready to bring to this new project the combined efforts derived from long interest and preparation, so with the early progress of regional enteritis. From the Mt. Sinai Hospital in New York, a detailed and comprehensive survey was reported in 1923 of 4 cases of nonspecific intestinal granulomas, including one of ileitis.[8] At the same hospital Ginz-

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burg and Oppenheimer had become interested in the pathology of these cases as they occurred in the small intestine. Crohn's clinical interest having been stimulated by the successful result obtained in his first case treated surgically, he joined forces with them in collecting, studying and describing 14 cases of enteritis limited to the terminal ileum.[1]

Pathology

In their first report, Crohn, Ginzburg and Oppenheimer[1] referred to regional ileitis as a pathological and clinical entity, though their description of the microscopical details did not reveal any specific features. The giant cells and groupings of large, pale cells in their vicinity were not considered essential, but rather accidental findings, representing a foreign-body reaction to encapsulated particles of vegetable matter trapped within the ulcers.

Although most observers have accepted regional enteritis as a distinct clinical entity, some dispute the additional claim to pathological specificity.[9]

Hadfield[10] considered the giant-cell systems found in the thickened submucosa and regional lymph nodes, and composed of epithelioid and several giant cells, characteristic and even specific of regional enteritis — to be distinguished from the foreign-body giant-cell type, which fuses with the adjacent inflammatory reaction. Warren and Sommers[11,12] described the specific pathological feature as proliferating endothelial cells within the lacteals immediately beneath the epithelium of the intestinal glands, as well as in the lymphatics, the submucosa and subserosa. This obliterative lymphangitis mechanically interrupts lymph flow. Surrounded by eosinophils and lymphoid cells, these conglomerate masses with giant cells form the noncaseating tubercle. A similar characteristic finding appears in the regional nodes. These primary changes, by pressure on the arterial lumen, result in inflammation and fibrosis. The secondary changes thus produced may then predominate in the microscopical picture and obscure the primary specific features that gave rise to them. The failure to find these primary features in all cases is explained by the fact that much of the surgical material available for examination is derived from patients with long-standing chronic disease, in whom the clinical consequences of these secondary changes were responsible for the operation.[13,14]

Even if one did not consider this microscopical description, in its isolated form, uniquely different from that found in sarcoidosis, in tuberculosis, or in reaction to foreign bodies such as lipids, talc and vegetable matter, its stereotyped occurrence, in association with the typical clinical picture, strongly suggests a clinical and pathological entity. Although no single feature may be pathognomonic of regional enteritis, the combination of the gross and histologic findings, viewed in relation to the recurring clinical pattern, defines a characteristic diagnostic term.

Liber[15] first described aberrant pyloric glands scattered throughout the small intestine in over 80 per cent of patients with regional enteritis. These glands resembled the Brunner type of mucus-producing glands hitherto found exclusively in the pyloric region. Since this first description, they have not been found under any circumstances in the colon, nor in any other condition of the small intestine, such as tuberculosis, postradiation enteritis or neoplasm. Prognostic value has recently been attached to this finding in that the incidence of recurrence after resection was directly related to the presence of these presumably metaplastic glands. Where no glands of the Brunner type were found in the resected specimens, there were no subsequent recurrences.[16]

Etiology

The etiology of regional ileitis is as confused and controversial as the clinical picture is clearly definable. It is sufficient to list the various theories suggested since 1932 as an indication of the unsettled nature of this problem.

Such a grouping would include trauma, allergy, foreign bodies, bacteria and anatomic variants resulting in impaired blood and lymphatic supply and drainage.[17] Only a few will be dealt with in some detail because of their promise or recent origin, but after all must be appended the verdict "not proved."

The similarity of elephantiasis, secondary to infectious lymphatic obstruction in the extremities, to the gross and microscopical picture of the bowel in regional enteritis was the basis for attempts to reproduce the disease in dogs.[18] Serial injections of crystalline silica or rosaniline dye into the mesenteric and subserosal lymphatics, after an earlier intravenous injection of *Escherichia coli*, resulted in edema in the submucosal and muscular layers, and accounted for a thickened bowel, pathologically similar to that of regional enteritis.

By analogy with the clinical production of silicosis through the absorption of silica by the lymphatics of the lung, it was believed that the lymphatics of the small intestine could absorb similar material, with consequent edema, thickening and fibrosis of the involved loop, mesentery and adjacent lymph nodes.[19] The mechanism of such observed gross and microscopical changes may be a property of certain substances, such as cholesterol, talc and silica (found in some toothpastes), which by virtue of the asymmetrical arrangement of atoms within their molecules develop a surface electric charge when subjected to pressure or an electromagnetic field. When absorbed through the lymphatics, they are capable of evoking a proliferative cellular response or granuloma.

Both these experiments, although they may not be an exact duplication of what occurs spontaneously in patients with regional enteritis, indicate a possible anatomic pathway over which various exciting factors

may travel. However, the primary role assigned to the lymphatics in this concept is not borne out by observations on acute mesenteric lymphadenitis, in which the small intestine is only rarely involved. Nor are the lymph nodes in acute ileitis more than locally abnormal.

As with ulcerative colitis, Felsen[20] related acute and chronic ileitis to the common etiologic background of an antecedent attack of bacillary dysentery. Among 29 cases, during an epidemic of bacillary dysentery, he observed acute inflammatory changes in the terminal ileum with edema and thickening, followed ultimately by the development of chronic ileitis in half. The importance of these findings should perhaps be limited to the conclusion that bacillary dysentery can contribute to the pool of patients with regional enteritis, but there is no proof from any confirmatory series that all or even any significant number are etiologically related to this specific agent.

The similarity of the tubercle in regional enteritis to that seen in sarcoidosis has led to an assumption of identity for the two conditions. Hadfield[10] was especially struck by this microscopical likeness. However, generalized sarcoidosis only rarely involves the intestinal tract and is not associated with fistulas or rectal complications.[21-23] Statistically, it cannot be considered an important source of regional enteritis.

The recent description of porcine ileitis in Denmark suggested on anatomic grounds a common distribution and pointed to a possible laboratory animal for reproduction of the disease by transfer experiment through inoculation or contact.[24-26] Such attempts have so far been unsuccessful, nor have any infectious agents been cultured. Whereas the thickening of the terminal ileum and enlargement of the swollen mesenteric nodes are similar to that seen in human beings, the absence of giant-cell systems and tubercles in porcine ileitis is a striking difference from the characteristic histologic picture in human ileitis.

The clinical fact that regional enteritis has been seen to develop after abdominal trauma stimulated efforts to reproduce the disease in dogs whose small intestine was subjected to the temporarily constricting effect of steel clamps.[27] The lesions produced did not resemble regional enteritis. Again, nonpenetrating trauma of a degree that is clinically recognizable and remembered by the patient does not statistically constitute an important factor, though it may sometimes precipitate progression in an otherwise inactive case of enteritis.

Acute Regional Ileitis

Crohn and his group[1] recognized acute ileitis as a phase of the chronic stage, though they definitely state that an unpredictable few patients have spontaneous resolution. In the ensuing years, the special part played by these acute cases has been clarified, especially so far as therapy is concerned.[28] The usual patient with regional enteritis gives a history of insidious onset with symptoms of two or three years' duration before medical attention is sought. In the acute cases the presence of diarrhea is not sufficiently peculiar to ileitis to eliminate consideration of appendicitis, which figures most frequently in the differential diagnosis. Surgical intervention, therefore, is often necessary to establish the diagnosis. Although there are those[29] who believe that most acute cases go on to develop into chronic disease, spontaneous resolution is sufficiently frequent to warrant expectant treatment beyond the exploratory laparotomy. The overall statistics indicate that 25 to 50 per cent subside without definitive surgical treatment.[30-32] In Van Patter's[33] series of 600 patients, 14 per cent dated the onset of their disease before the age of fifteen. The current view regarding acute ileitis, limited to the terminal ileum, is to entertain the possibility of spontaneous resolution, with expectant conservative treatment as the keynote. Surgery should be limited to an exploration when necessary to establish a definite diagnosis, since most cases of abdominal fistula have followed an appendectomy, in which the terminal ileum is acutely inflamed. Unfortunately, an unpredictable percentage will go on to present the usual features of chronic enteritis, if the follow-up study is adequate. The significance of these conclusions must be evaluated in the light of the fact that the diagnosis of acute ileitis, even when exploration is undertaken, is made on clinical grounds and gross inspection, without benefit of confirmation by histologic examination of resected specimens. The possibility of confusion with mesenteric adenitis, intestinal allergy, tuberculosis and lymphoma cannot be disregarded.[34]

Granulomatous Involvement of Stomach and Duodenum

The extension of granulomatous involvement beyond the confines of the ileum and jejunum has most recently embraced the stomach and duodenum. The clinical features are peculiar to the location involved and include gastric retention with nausea, vomiting and epigastric distress aggravated by food, malabsorption, anemia and hypoproteinemia. When found in association with involvement of the ileum, the clinical picture is compounded of the effects of such diverse location and function. The diagnosis is suggested by exclusion not only of the usual conditions considered in the differential diagnosis of regional enteritis in its more common aspects but also of obstructive lesions peculiar to the pyloric and duodenal region, such as ulcer and carcinoma. Although ulceration in the granulomatous area is common and fistula formation is rare, the histologic lesion is similar to that seen in regional enteritis elsewhere.

Because of the location of the lesion, with predominance of obstructive signs, conservative measures have not been successful. Short-circuiting procedures

with gastroenterostomy may offer the best therapeutic results if the anastomosis is not made through granulomatous tissue.

By 1955, 20 cases involving the stomach or the duodenum or both had been recorded.[35-39]

Ileojejunitis

Involvement of the jejunum in association with ileitis, or as an isolated granulomatous lesion, was very soon recognized and reported after the original description of terminal ileitis—necessitating revision of the terminology to the more inclusive name of regional enteritis.[4,5] In its most frequently observed form, the jejunal process is associated with universal involvement of the ileum, with which it is continuous. Isolated involvement of the jejunum is much less frequent — approximately 80 cases having been reported in the literature up to 1950.[40] This type is to be differentiated from that observed as a sequel to successive resections of ileum when the jejunum is incorporated in the anastomosis and shares in the proximal extension of the disease.

The greater area of involved bowel is responsible for the severe constitutional reaction. In spite of a lessened tendency to fistula formation, malabsorption is a prominent feature, and may be reflected in retarded skeletal growth, macrocytic anemia, prothrombin deficiency and tetany. The diffuseness of the process militates against the advisability of resection and enhances the importance of patient, conservative therapy aimed at maintaining nutrition and combating infection. The specific x-ray configurations are referred to below in the section on roentgenographic studies.

Ileocolitis

It is not intended to discuss here the controversy about the common etiologic relation of regional enteritis and ulcerative colitis. In most cases, such a kinship is not suggested by the characteristic anatomic distribution, pathological findings or roentgenographic picture. Ulcerative colitis of universal involvement does not extend beyond the ileocecal valve, except as a backwash phenomenon in approximately 20 per cent of cases.[41] This rate may be as high as 40 per cent with right-sided colitis. The frequency of this association must be considered, if surgery is to remove all disease in the bowel. The ileum incorporated in this contiguous inflammatory process may, in most cases, be distinguished pathologically from primary terminal ileitis,[12] the rigidity and narrowing of which is seldom seen. Rather, the picture in backwash ileitis is one of mucosal ulceration with varying degrees of distensibility. The absence of fistula formation and pressure defect on the adjacent cecum also helps distinguish this group from terminal ileitis. Similarly, regional enteritis crosses the same ileocecal barrier into the colon in less than 10 per cent of cases; there may be simultaneous involvement of the terminal ileum and colon, or one may follow the other after surgery for either. Here, too, the pathologic process is distinct for the two areas involved — the fibrosing, granulomatous involvement of all the layers in the small intestine, as opposed to the ulcerative, exudative process, primarily limited to the mucosa and submucosa in the colon.

Only very rarely does one find an identical granulomatous involvement in the ileum and colon.

Roentgenographic Studies

The diagnosis may be suspected strongly and, at times, established on clinical grounds. More often, careful roentgenographic examination not only will confirm the nature, stage and extent of the lesion, but also may represent the only clue to an otherwise obscure cause of fever, diarrhea, anemia or malnutrition.

The string sign, a term first used by Kantor[42] to describe the cotton-string appearance of the narrowed lumen of the terminal ileum, remains the oldest of the characteristic signs of regional enteritis. Borrowed from a similar term used to describe the attenuated bowel of spastic colon, it is not pathognomonic of this disease, since it may also be seen, though much less frequently, in ileocecal tuberculosis and sarcoma. Even more important is the realization that the string sign, like its precursor, does not always represent a fixed, rigid, burnt-out process, amenable to successful surgery, without much risk of recurrence. The variable nature of this x-ray configuration may be due to the inconstant spasm and irritability associated with ulceration, and surgery undertaken under these mistaken and inauspicious circumstances is often responsible for progression and recurrence in an active process.

In their initial description, Crohn et al.[1] limited their discussion of the roentgenographic appearance to a description of the negative findings in the colon and disturbances of motility, with stenosis, puddling, distention and fistula formation in the small intestine.

The study of this most frequent and important nonspecific inflammatory disease of the small intestine has led to many fundamental conclusions concerning the normal variants in roentgenographic configurations in this segment. It has also led to a clearer correlation of their graphic representation with the clinical and pathological stage of the disease, the extent and depth of its spread and amenability to surgical therapy.

Various classifications have been suggested for a more systematic grouping — on the basis of chronology or gross pathological features. Any attempt to describe the earliest changes must be subject to the reservation that the patient rarely presents himself for examination before the process has become well established. Observations made early in the clinical

course, and at the site of recurrent activity after exclusion operations, may simulate the roentgenographic appearance of the initial lesion. Even here, as in any stage that appears clinically acute, one may be dealing only with an exacerbation or the reactivation of a chronic process.

Not only is it more feasible to separate these cases in relation to their stenotic quality but also the therapeutic implications of such a division are clinically expedient and sound. In the nonstenotic phase, as clearly set forth by Marshak and Wolf,[43] the earliest changes observed consist of blunting and thickening of the mucosal folds, which lose their regular appearance as they become partly fused. With destruction of the valvulae conniventes, the lumen becomes variable in width, and the mucosa granular, especially in the jejunum. With further progression of the ulcerating process, the bowel resembles a tubular cast, owing to complete disappearance of any mucous-membrane pattern. This picture is at first flexible and varying in the degree of narrowing and mucosal pattern until the edematous thickening and spasm give way to the fixed rigidity and fibrosed constriction of the stenotic phase.

In this stage, the lumen is markedly narrowed over varying lengths of bowel, producing proximal dilatation. Within this dilated area, the secondary changes of hypertrophy and retained secretions may simulate active disease and unjustifiably preclude any attempt at surgical therapy because of an exaggerated estimate of the extent of bowel involvement.

In addition to the general characteristics described above, there are some peculiar to the different segments of the gastrointestinal tract. The string sign of the terminal ileum has already been alluded to, including the various and possible components of its roentgenographic appearances and their effect on the therapeutic approach. Ulcerations and their sequelae of perforation and fistula formation are more frequent in the ileum than elsewhere. Isolated involvement of the jejunum and duodenum is associated with prominence of the stenotic phase and infrequency of ulceration and fistula formation. Such findings lend themselves to successful treatment by sidetracking operation, since the paucity of ulceration lessens the chances of recurrence. This observation, which generally holds true for enteritis wherever it occurs, emphasizes the value of accurate delineation of these phases — stenotic and nonstenotic. Recurrent enteritis is less common if exclusion or resection is undertaken when the disease has reached the healing stage, with obstruction due to thickening and constriction, rather than at a time when ulceration and fistula formation are indications of continued activity.

The linear extent of the bowel involvement seldom changes after the patient appears for the first roentgenographic examination. Qualitative changes within this relatively fixed length are usually reflected in the complications of stenosis and fistula. The major exception to the static quantitative aspect of this progression is the frequent recurrence observed, usually within the first year, after surgery.

Complications

Attention is given here only to the few complications that have been noted and emphasized since Crohn's original report. Of foremost interest is the frequent finding of anorectal and perirectal abscesses and fistulas, which were specifically excluded in the description of the clinical features of the first 14 patients.[1] These complications have come to be recognized as among the most common signs of the disease, seen in appproximately 25 per cent of cases and often preceding the other manifestations.[28,33,44] Derived from the involved ileum by direct extension or, more commonly, by way of infected crypts of Morgagni, they usually require some form of surgical intervention, at times even a diversionary ileostomy. In the differential diagnosis of these abscesses and fistulas, ulcerative colitis is the most important disease to be considered.

Less frequently encountered, and seldom suspected because of their extraintestinal location, are disturbances of the urinary tract. In 4 to 10 per cent of patients with regional enteritis, it has been estimated that urologic complications may be present, varying from those which are asymptomatic and visible only with special technics to those presenting with clinically obvious urologic disease.[45,46] Among these are enterovesical fistulas, retroperitoneal abscesses and ureteral narrowing or actual obstruction, with hydroureter and hydronephrosis, primarily involving the right side.

Of interest is the recent incidental finding in at least 4 patients of an unsuspected nodular enlargement of the pancreas, without any apparent associated clinical significance.[47] It is especially noteworthy that the last 3 cases were detected within a short interval after attention had been called to such a possibility by the first demonstration.

Emotions, Psyche and Regional Enteritis

The same controversy exists as in ulcerative colitis concerning the relation between psychologic disturbances and organic changes in regional enteritis. The evidence for and against the psychogenic basis of colitis has been presented in detail,[48,49] and essentially the same views are held for regional enteritis. Studies purporting to show neither characteristic personality profile nor greater incidence of anxiety than among comparable groups of patients with other diseases, and denying the etiologic relation between emotional stress and regional enteritis,[50] have been attacked as the result of impressions derived from inadequate history taking and superficial observations.[51] As with ulcerative colitis, some have found, on intensive psychiatric interviewing, that the repetitious impact of stressful life situations on physiologic functions may eventually

produce the structural abnormalities of regional enteritis and that disturbing aspects of the environment can be correlated clinically with exacerbations of the disease. Whether or not one agrees that psychosomatic factors are more important in affecting the course of regional enteritis than that of ulcerative colitis, one cannot ignore the need for considering these factors in treating patients with this disease. Whether of primary etiologic importance, or the secondary effect of long-standing debilitating sickness with anemia and malnutrition, sympathetic care, understanding and support of emotional needs represent an important adjuvant to the unimpressive results of therapy directed only to the physical inadequacies.

(To be concluded)

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MEDICAL INTELLIGENCE

BENIGN ENLARGEMENT OF THE MALE BREAST*

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BOSTON

VARIOUS methods of management of gynecomastia have been recorded in detail in the literature,[1-11] but none of the authors have sufficiently stressed conservative treatment. This article discusses 351 cases of benign enlargement of the male breast in 307 patients treated at the Tumor Clinic of the Massachusetts General Hospital, the Huntington Hospital and the Pondville State Hospital. None of the 307 patients had any sexual abnormalities or endocrine or liver dysfunction. Patients who had been on stilbestrol or estrogen therapy are not included.

The exact frequency of mammoplasia in the male is unknown. Since the process is usually self-limited, relatively few patients consult a physician.

Clinically benign enlargement of the male breast is characterized in 90 per cent of cases by a rubbery, discoid, subareolar plaque of tissue, which is freely movable and not adherent to the skin or underlying tissue. This enlargement has been termed adolescent mammoplasia in the young male and senescent mammoplasia in the older age group. When the breast swelling is uniform and assumes the configuration of the female breast, the term gynecomastia is applied.

Mammoplasia in the male is probably related to gonadal activity and temporary hormonal imbalance. In the present series the peak incidences correspond with puberty and advancing age, when marked hormonal changes occur in the sexual organs.

Lewis and Geschickter[1] have pointed out the great frequency of gynecomastia in hermaphrodites, pseudohermaphrodites and patients with teratomas of the testes. Klinefelter, Reifenstein and Albright[2] reported cases of gynecomastia associated with azoospermia and small testes without aleydigism.

Jacobs[3] has reported on gynecomastia in prisoners of war. During starvation the breasts were normal, but as the men resumed eating a full diet, gynecomastia appeared. Jacobs has pointed out that during starvation the production of sex hormones is greatly decreased. When normal feeding is resumed the gonads secrete testosterone and estrogen. However, the liver that was damaged during starvation is able to inactivate testosterone but not estrogen. Gynecomastia results. The presence of enlargement of the breast in male patients with hepatic cirrhosis, in which there is impaired deactivation of estrogen, is well known.

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AGE DISTRIBUTION

In this series the youngest patient was twelve, and the oldest eighty-four years of age (Table 1).

Every age between the two extremes was represented. The group between twelve and nineteen years inclusive was the largest, with 115 cases. In the third, fourth, and fifth decades there was a decline, with a rise in incidence after the age of fifty.

TABLE 1. *Distribution of Mammoplasia According to Age.*

AGE	NO. OF CASES
yr.	
12-21	136
22-31	34
32-41	35
42-51	33
52-61	45
62-71	40
72-81	24
82-91	4

SIGNS AND SYMPTOMS

The patients when first seen usually complained of a lump or swelling. Pain and tenderness were symptoms in only a few cases. Fifty-five per cent of the enlargements were on the left, and forty-five per cent on the right. Sometimes, bilateral swelling was present. The subareolar plaques, which were rubbery, discoid and freely movable, varied from 1 to 10 cm. in diameter. In a few cases examination revealed small or atrophic testes. Urinary ketosteroid excretions were studied in some patients, and the values obtained were within normal limits.

ETIOLOGY

Trauma or infection did not appear to be involved, a history of the former being obtained in a very few cases. The trauma probably helped to call attention to a pre-existing lesion. No patients had the signs associated with an infectious process.

TREATMENT

Before 1943 the treatment in this series was excision in many cases. In this manner a definite diagnosis

was established, and cancer ruled out. The members of the staff of the tumor clinics at Massachusetts General and Pondville hospitals were impressed by the number of spontaneous regressions. A policy of expectant treatment was established.

In no case was a malignant lesion of the breast confused with adolescent or senescent mammoplasia. Regression in over 80 per cent of the 228 cases treated conservatively resulted after an interval of one month to two years. The average time was approximately six months.

The criteria for surgical treatment are as follows: cases that cannot be followed (this is more applicable to older age groups); sensitive males who may be psychically disturbed; failure of any sign of regression after a period of one or two months of observation; suspicion that the enlargement may be malignant — surgical treatment is certainly indicated if the lesion is hard or if there is dimpling of the overlying skin or nipple retraction; and pseudogynecomastia, which is an abnormal amount of fat in the breast, surgical excision being done for cosmetic reasons.

Histologic examination of the specimens removed at operation revealed an increased amount of ductal and connective-tissue elements.

Hoffman[4] and Adair[5] have advocated testosterone for benign enlargement. Only a few of their cases responded to hormonal treatment. Some of the cases in this series were treated with testosterone, with disappointing results. In 1 patient receiving testosterone mammoplasia began to recede in the involved breast, but the opposite breast enlarged. The members of the staff believed that breast enlargement responding to androgens would subside spontaneously.

Conclusions

Adolescent or senescent mammoplasia is usually self-limited. Spontaneous regression results in most cases. The enlargement of the breast is physiologic and probably due to a temporary estrogen-androgen imbalance. The condition, a common phenomenon, is not precancerous. The treatment of choice is expectant, and surgical treatment is indicated only for a few cases. Androgen therapy has been unsatisfactory.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42211

PRESENTATION OF CASE

A fifty-seven-year-old woman was admitted to the hospital because of headaches.

Four years previously she noted that after exposure to cold her hands became white and numb. Seven months before entry this phenomenon also began to occur in the big toes. At this time difficulty in mastication, dysphagia, thickening and tightness of the skin of the hands and slight aching in the joints of the hands without associated redness, swelling or tenderness were noted. The blood pressure several months later was said to have been 150 systolic. Five weeks before admission severe, throbbing headaches in the frontal, parietal and occipital regions were noted. The headaches, which subsequently varied in intensity, persisted until the time of admission. Two weeks later, when she was climbing a hill, there was an episode of severe dyspnea that was relieved by rest. Paroxysmal nocturnal dyspnea occurred each night for about a week afterward. There was no palpitation, nor was there chest pain or ankle edema. Two weeks before entry, while she was lying in bed, there was an episode of sudden dyspnea associated with marked cyanosis of the face and blanching of the hands. She was admitted to another hospital, where the blood pressure was noted to be 218 systolic, 100 diastolic. Examination of the blood revealed a hemoglobin of 10 gm. per 100 ml. and a white-cell count that ranged between 11,600 and 15,000, with a normal differential. The nonprotein nitrogen was 45 mg. and subsequently rose to 90 mg. per 100 ml. An x-ray film of the chest demonstrated cardiac enlargement, and an electrocardiogram showed nonspecific changes. With digitoxin and Mercuhydrin therapy the dyspnea was relieved, but the hypertension persisted in spite of Serpasil and Apresoline, which were given for four days. Two days before entry persistent blurring of vision and "yellow vision" were noted, and the headaches became more severe. On the next day there was nausea, with retching and belching.

There was no past history of hypertension, renal disease, edema, skin rash, fever or chills. Thirty years previously the patient gained 30 pounds in weight during her first pregnancy, which was otherwise uneventful.

Physical examination showed an alert, obese, moon-faced woman in no distress. There was a striking, wooden quality to the skin, especially over the face, hands and distal portions of the forearms, although she was able to squeeze the hands tightly and to smile. The hands were slightly contracted and nontender, with nonpitting edema and slight erythema. Raynaud's phenomenon was not observed after the hands were placed in ice water. Slight distention of the neck veins was noted. Examination of the optic fundi revealed severe vascular disease, with narrowing and tortuosity of vessels and with a copper-wire appearance, segmentation and arteriovenous nicking; there were numerous exudates and small, flame-shaped hemorrhages; the optic disks were blurred but not elevated. The heart was slightly enlarged to the left. The pulmonic second sound was greater than the aortic. The first mitral sound, which was split, was clear and loud. A soft, Grade 1 systolic murmur was audible at the base. The lungs and abdomen were normal.

The temperature was 99°F., the pulse 88, and the respirations 18. The blood pressure was 240 systolic, 122 diastolic, in the right arm and leg and 248 systolic, 128 diastolic, in the left.

The urine gave a + + test for albumin and had a specific gravity of 1.020; the sediment contained 10 red cells, 5 to 10 white cells and many granular casts per high-power field. Examination of the blood revealed a hemoglobin of 12.5 gm. per 100 ml., a white-cell count of 19,400, with 70 per cent neutrophils, and a sedimentation rate of 0.48 mm. per minute. The nonprotein nitrogen was 100 mg., the total protein 5.8 gm., the albumin 4.2 gm., the globulin 1.6 gm., the calcium 9.6 mg., the phosphorus 5.5 mg., the cholesterol 232 mg., the creatinine 3.7 mg., the bilirubin 0.3 mg., and the fasting blood sugar 118 mg. per 100 ml. The serum sodium was 132 milliequiv., the potassium 4.3 milliequiv., the chloride 95 milliequiv., and the carbon dioxide 27 milliequiv. per liter. The serum electrophoretic pattern was normal. The alkaline phosphatase was 1 unit, and the prothrombin content was 67 per cent. Cephalin flocculation was negative in forty-eight hours. Two "L-E" preparations and a blood Hinton test were negative. A Regitine test was negative. A culture of the throat grew out a few nonhemolytic streptococci, *Staphylococcus albus* and alpha-hemolytic streptococci. X-ray films of the chest demonstrated prominence of the

left ventricular portion of the cardiac shadow and tortuosity of the aorta, with calcification in the ascending portion, arch and descending portion; fluoroscopically, cardiac pulsations were normal. Films of the hands were normal. An upper gastrointestinal series showed some degree of delay of passage of the barium through the esophagus, with irregularity of peristaltic contractions; the stomach, duodenum and jejunum were normal. An electrocardiogram showed a normal sinus rhythm at a rate of 90; the PR and QRS intervals were 0.16 and 0.07 second, respectively; the axis was normal; the ST segments were slightly depressed in Leads 1, 2, aVF, V_5 and V_6; the T waves were low or inverted in all leads.

With omission of digitoxin the nausea and "yellow vision" subsided although vision remained poor. On the fourth hospital day the specific gravity of the urine was 1.010, the creatinine clearance was 28 liters per twenty-four hours, and a phenolsulfonphthalein test showed 3 per cent excretion in fifteen minutes and 15 per cent in two hours. Two days later the patient had hallucinations. The fasting blood sugar was 135 mg. per 100 ml. The serum sodium was 139 milliequiv., the potassium 4.6 milliequiv., and the total solutes 300 milliosmols per liter and the total urine solutes 302 milliosmols per liter. Subsequently, there were episodes of dyspnea that were accompanied by basal pulmonary rales and relieved with aminophylline. Digitalis therapy was begun. On the ninth hospital day the veins of the neck were noted to be more distended and pulsating. Vision gradually worsened until there was complete blindness. A generalized convulsion occurred on the next day. The blood pressure after this episode was 190 systolic, 100 diastolic. An electroencephalogram was markedly abnormal, with diffuse high-voltage slowing. There was progressive mental deterioration, with paranoid behavior. On the eleventh hospital day the creatinine clearance was 5.3 liters per twenty-four hours.

The patient noted some aching in the chest anteriorly on the twelfth hospital day. The serum sodium was 120 milliequiv., the chloride 83 milliequiv., and the carbon dioxide 24 milliequiv. per liter. In spite of saline solution given intravenously, with return of the serum sodium to normal, there was no improvement in the mental status. Protoveratrine therapy was begun. There was no effect on the blood pressure until the next day, when, thirty minutes after the administration of 0.7 mg. of protoveratrine, the blood pressure fell to 100 systolic, 60 diastolic, and the patient became comatose. An electrocardiogram showed a sinus bradycardia with first-degree heart block. A lumbar puncture yielded 6 ml. of clear, acellular fluid under an initial pressure equivalent to 220 mm. of water and a final pressure equivalent to 190 mm.; the Pandy test was negative; the total protein was 54 mg. per 100 ml., and the gold-sol curve 1121110000. With oxygen, shock blocks, atropine, Neo-Synephrine and Wyamine the blood pressure returned to previous hypertensive levels, and she became slightly responsive. An electrocardiogram then showed a normal sinus rhythm at a rate of 70; the PR and QRS intervals were 0.20 and 0.08 second, respectively; the axis was normal; there were RR′ waves in Leads V_1 through V_3 and tall R waves in Lead V_5. In spite of Dilantin, convulsions as well as dyspnea and cyanosis continued. The temperature ranged between normal and 102°F. On the fifteenth hospital day an electrocardiogram demonstrated a normal sinus rhythm at a rate of 80; the PR and QRS intervals were 0.18 and 0.08 second, respectively; the axis was normal; QS complexes were present in Lead V_1; QR complexes with a high ST origin were present in Lead V_2; RS waves with slight ST elevation were present in Lead V_3; there were small S waves in Leads V_5 and V_6. She died two days later. Terminally, there was oliguria, increasing dyspnea and further elevation of the white-cell count to 45,600, with 87 per cent neutrophils; the serum nonprotein nitrogen rose to 220 mg. per 100 ml.

Differential Diagnosis

Dr. Max Rosenheim*: This fifty-one year old woman was in the malignant phase of hypertension on admission. She had gross retinal changes and progressive renal failure with convulsions, coma and death. We now use the term malignant "phase" rather than malignant hypertension because we believe that a malignant phase can appear in almost any form of hypertension provided it is severe enough. The clinical definition differs from that of the pathologists in that it is made on retinal signs: the presence of blurring of the disk in association with severe arterial changes, hemorrhages and exudates. The pathologist, when he makes a diagnosis of malignant phase, implies the presence of necrotizing arteriolitis or fibrinoid necrosis in the arterioles, especially of the kidneys.

What was the cause of the severe hypertension? The first possibility to be considered is essential hypertension. It is noteworthy that in this long history there was no mention of the family history.

Dr. Benjamin Castleman: The mother died at the age of seventy of an enlarged heart, and that is all the information given. There was no history of hypertension in the other members of the family.

Dr. Rosenheim: I shall be able, then, to fall back on the mother's large heart if need be to bring in essential hypertension. I should say that this is, however, unlikely. When the patient was first seen, the blood pressure was 150 systolic, and it rose quite

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rapidly, passing into the malignant phase. It is unusual for benign essential hypertension to pass into the malignant phase in a patient fifty-seven years of age.

Was there an endocrine cause? She may have had secondary Cushing syndrome from cortisone, but I should not have thought from the history that she had the primary disease. There was no clear history of renal disease in the past to suggest an underlying primary renal condition. The history really gives no clue to the etiology of the hypertension.

There was a four-year history of Raynaud's phenomenon. This does not start in a woman at the age of fifty-seven on the basis of spasm of the digital arteries. I note the statement that the hands were affected. In the ordinary Raynaud phenomenon seen in a young girl the whiteness of the hands stops sharply at the base of the fingers. In scleroderma at an early stage, the attack spreads to the back of the hand and as far as the wrist. I think, therefore, that the history of Raynaud's phenomenon affecting the hands is suggestive of scleroderma. The thickening of the skin of the hands and face, the aching in the joints, the difficulty in mastication, the dysphagia and the fact that the toes were affected are additional evidence of scleroderma. This condition is most frequently seen in middle-aged women and is more common in women than in men. On the basis of the history alone I should make a definite diagnosis of scleroderma.

Scleroderma is a generalized collagen disease. As Cecil and Loeb[1] say, "the cutaneous lesions are merely the external manifestations of a systemic disease." Goetz[2] has suggested that it should be called "progressive systemic sclerosis" rather than scleroderma. Hale and Schatzki,[3] at the Massachusetts General Hospital, wrote the classic paper about the involvement of the alimentary tract in this condition. The symptoms of difficulty with mastication and dysphagia, which this patient had, are typical of involvement of the esophagus with scleroderma. According to the paper by Hale and Schatzki one would expect to see delayed emptying, decreased peristalsis and some dilatation of the esophagus.

The heart is also frequently involved in scleroderma. Some of the patient's symptoms, signs and findings may well have been the result of scleroderma heart disease. She was dyspneic and had orthopnea and cyanosis. The electrocardiogram repeatedly suggested myocardial damage. The classic paper about scleroderma heart disease also comes from this city, a paper of Soma Weiss and his colleagues, Stead, Warren and Bailey,[4] in 1943.

This, then, was a case of scleroderma with alimentary-tract involvement and with possible scleroderma heart disease. Can one explain the hypertension in terms of the heart disease? In the heart, I should expect to find gross changes in the myocardium with fragmentation of some of the fibrils. It would be difficult to conceive that those changes in the myocardium could produce hypertension. Some of Soma Weiss's patients had moderate, and none had severe, hypertension. I note that the pulmonic second sound was greater than the aortic in this patient with severe hypertension. This is unusual, and the question of pulmonary disease, possibly the pulmonary fibrosis that occurs in scleroderma, might be raised. I should not, however, be so rash as to make a diagnosis of pulmonary involvement on the basis of a loud pulmonic second sound alone.

The hypertension and renal failure, I take it, were the real problems in this sclerodermatous patient. Scleroderma renal disease has frequently been described (by Bevans[5] and Moore and Sheehan[6]) and shows changes similar to those seen in the kidneys with other collagen disease, particularly disseminated lupus erythematosus. In the urine of this patient albumin, red cells and casts were present. When she was first admitted to the hospital the urine had a specific gravity of 1.020 although the nonprotein nitrogen was raised. These findings suggest either extrarenal azotemia or an acute glomerular lesion. They are the sort of findings seen in acute glomerulonephritis. She may, therefore, have had acute glomerular lesions of scleroderma. Changes in the fundi such as are described in the case history are rare in scleroderma, but certainly occur in polyarteritis nodosa and disseminated lupus erythematosus. In these two conditions, which are closely related to scleroderma, exudates appear quite early, arterial changes are seen, and the malignant phase of hypertension may develop. The characteristic findings in the kidneys in scleroderma are glomerular damage, fibrinoid necrosis, degeneration and sometimes "wire-loop" changes. There have been one or two papers reviewing such renal lesions, but I have found only one report of a patient who had severe hypertension associated with the uremia (Platt and Davson[7]).

My clinical diagnosis, then, is scleroderma, with scleroderma heart disease, scleroderma renal disease, malignant hypertension and renal failure. The terminal course, which was dramatic, may well have been caused by cerebral edema and hypertensive encephalopathy. Cerebrovascular lesions have been described in scleroderma, but I shall not add involvement of the brain or lungs with scleroderma to my clinical diagnosis.

Did the patient receive cortisone? It is difficult to believe that in 1956 a patient would be allowed to die of scleroderma without steroid therapy. She certainly had a great many other types of therapy, and I imagine that she had steroid therapy. The only clue is the use of the curious adjective "moon-faced" on admission.

DR. CASTLEMAN: She did not receive any cortisone. At Arthritic Rounds the entire group, including Dr. Ropes, were opposed to steroid treatment because

of the uncertain diagnosis of renal disease and its potential harm.

DR. ALFRED KRANES: Every now and then we see patients with the clinical syndrome of either lupus erythematosus or scleroderma and yet the pathologist tells us he finds the lesions of polyarteritis nodosa. Do you think it possible that, in spite of the clinical evidence of scleroderma, the renal lesions were those of polyarteritis?

DR. ROSENHEIM: The patient with severe hypertension associated with classic scleroderma described by Platt and Davson[7] had renal lesions suggestive of polyarteritis. I think the name given to the disease depends on the pathologist.

DR. MARIAN W. ROPES: We had the same questions about the possible causes of the hypertension. The opinion was greatly divided, with a majority thinking that it was probably related to the underlying scleroderma. Many of us, however, wondered whether there might not have been a separate renal disease. This problem remains of great interest; the evidence for the possibility of renal involvement in scleroderma has been accumulating recently.

DR. EVAN CALKINS: Some of the reports on scleroderma kidney disease describe an arterial lesion in the interlobular arteries in the kidneys with marked thickening of the intima in addition to the changes that Dr. Rosenheim mentioned. If these lesions are seen on microscopical examination I wonder whether that would lend support to scleroderma kidney disease.

CLINICAL DIAGNOSES

Scleroderma, with involvement of skin, esophagus, heart, kidneys and ? central nervous system.
Uremia.
Hypertension, malignant.

DR. MAX ROSENHEIM'S DIAGNOSIS

Scleroderma, with scleroderma heart and kidney disease.

ANATOMICAL DIAGNOSES

Scleroderma.
Scleroderma renal disease.
Necrotizing arteriolitis of kidneys and pancreas.
(Uremia.)
Uremic colitis.
Cardiac hypertrophy.
(Malignant hypertension.)

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The kidneys were mottled, with many gray areas scattered throughout—an appearance that is very suggestive of malignant nephrosclerosis. In addition there were larger, yellowish areas that suggested infarction. The cut surface revealed areas of hemorrhage in the pelvis and into the cortex in streaks, indicating a great deal of necrosis as well as hemorrhage in the kidney. The yellowish areas suggested cortical necrosis of the kidneys as a result of ischemia. Microscopically, the streaks of hemorrhage in the cortex proved to be arterioles, with necrosis in the walls and extravasation of blood. There

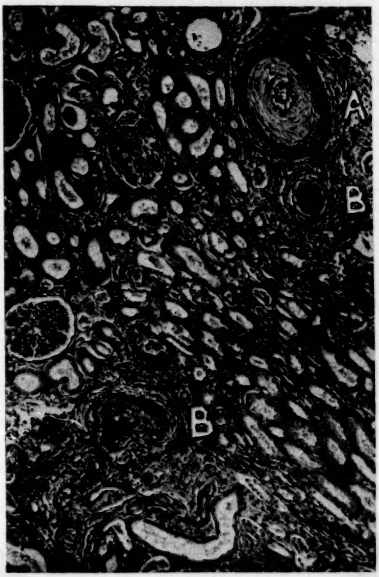

FIGURE 1. *Photomicrograph of the Kidney.*
A=*interlobular artery, with marked intimal proliferation.*
B=*necrotizing arteriolitis, with thrombosis.*

was fibrinoid necrosis in the small arteries and arterioles. Some of the glomerular tufts were perfectly normal; parts of others were necrotic. The fibrinoid necrosis was extensive, often involving the entire walls, and had produced thrombi. The many areas of infarction within the kidney were hemorrhagic. The lumens of the interlobular arteries, as predicted by Dr. Calkins, were filled with marked intimal mucoidlike proliferative changes (Fig. 1). We have seen this picture once before in the case reported from this hospital by Talbott et al.[8] in 1939. They likened the mucoidlike proliferation in the intima to Wharton's jelly. In many of these arteries the marked intimal proliferation reduced the lumens to mere pin points. There was some hemorrhage into the tubules.

This picture, I think, is characteristic of scleroderma kidney. Moore and Sheehan[6] reported 3 cases a few years ago, all with the same two types of changes:

the interlobular arteries had the intimal proliferation that apparently is the first stage and produces an ischemia of the kidneys that may continue for some time without producing symptoms; then, for some reason, the process suddenly progresses, arteriolar necrosis develops, and death occurs in uremia, usually within a month. It is interesting that in the case reported by Talbott et al.[8] in 1939 there was no hypertension even though the same changes were observed. Of the 3 patients of Moore and Sheehan[6] 1 had mild hypertension, and the other 2 did not. I suppose the degree of involvement determines whether or not hypertension appears as a terminal phase.

The only other organ in which we were able to find fibrinoid necrosis of the arteriolar walls was the pancreas. This was also associated with focal necrosis and areas of acute pancreatitis, undoubtedly the result of the occlusion of the arterioles.

Sections of the skin revealed the characteristic changes of scleroderma. There was uremic colitis, with marked vascular engorgement. We were unable to find lesions in the arterioles in the bowel that might account for the changes.

The heart was slightly hypertrophied and did not show much disease. The muscle fibers were slightly separated; in one or two sections we found slight fibrosis that looked like the type seen in a collagen disease, but it was not widespread. The lungs did not show the scleroderma picture.

A PHYSICIAN: What did the brain show?

DR. CASTLEMAN: Dr. Richardson, do you have any comment about the brain?

DR. EDWARD P. RICHARDSON, JR.: Grossly, the brain was of normal size and weight. On section the only abnormality was a small focus of hemorrhagic infarction in each occipital lobe. A preliminary set of microscopical sections showed the infarct to have been very recent—scarcely more than twenty-four hours old. Sections from representative areas of the brain did not show the arteriolar changes that were seen in the kidneys.

DR. KRANES: Did you examine the lower end of the esophagus?

DR. CASTLEMAN: Yes; we made a number of sections of the esophagus but were unable to find any evidence of scleroderma there or anywhere else in the gastrointestinal tract.

A PHYSICIAN: Was there much papilledema?

DR. CASTLEMAN: We took sections from the retina, which showed a few tiny hemorrhages, but that was all. I was not able to find any true necrosis of the arterioles there.

DR. CALKINS: I wonder if it might not be worth recording that a number of patients with scleroderma kidney disease who were treated with cortisone rapidly deteriorated. That fact influenced us in believing that it was not wise to give it to this patient.

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CASE 42212

PRESENTATION OF CASE

A sixty-eight-year-old woman was admitted to the Brockton Hospital because of melena.

Nine months previously there was an episode of severe abdominal pain in the right upper quadrant, with nausea, vomiting, dark urine and light-colored stools. A tender mass that subsequently disappeared spontaneously was palpable in the right upper quadrant. No similar episodes occurred. Six weeks before admission the patient had mild diarrhea without melena. For three days before entry there was slight nausea. Two days before admission she began to pass soft stools every two hours. One hour before entry there was sudden severe pain in the region of the umbilicus. She then passed three stools, which contained a total of about 500 ml. of blood. There was associated diffuse sweating and one episode of vomiting but no hematemesis.

For about two years the patient had had diabetes mellitus that was well controlled with diet and insulin. Fourteen months previously an abscess of the knee joint was incised and drained, and a septicemia caused by *Staphylococcus albus* was successfully treated with massive doses of penicillin. An electrocardiogram was interpreted as demonstrating myocardial fibrosis.

Physical examination showed a thin, pale, apprehensive woman. The heart was enlarged to the left. A Grade 2 apical systolic murmur was audible. Examination of the abdomen revealed a tender mass measuring about 10 cm. in diameter just above the umbilicus and toward the right side. The mass was not separable from the liver. The spleen was not felt. Rectal examination was negative except for the presence of bright-red blood.

The temperature was 98°F., the pulse 88, and the respirations 20. The blood pressure was 210 systolic, 110 diastolic.

The urine gave a +++ test for albumin; the sediment contained numerous white cells; culture

grew out coliform bacilli. Examination of the blood revealed a hemoglobin of 8.9 gm. per 100 ml. and a white-cell count of 9500. The fasting blood sugar was 159 mg. per 100 ml. The alkaline phosphatase was 6.4 units. The prothrombin content was 100 per cent. Bromsulfalein retention was 30 per cent after thirty minutes. X-ray films of the chest showed no significant changes. An upper gastrointestinal series showed a deformity of the second portion of the duodenum caused by an extrinsic pressure defect. A Graham test failed to visualize the gall bladder. Barium-enema examination was negative except for sigmoid diverticula.

On the ninth hospital day a cholecystostomy was performed. A markedly dilated, thickened gall bladder filled with numerous calculi was found. There were dense fibrous adhesions between the gall bladder and surrounding structures. The calculi were removed, and a biopsy of the liver showed minimal focal chronic cholangitis. Nine days later blood was noted oozing from the cholecystostomy tube. Because of continued bleeding the tube was removed. On the eleventh postoperative day there was an episode of hematemesis, and the temperature rose to 104.4°F. After gastric intubation and suction there was no further vomiting. Thereafter, the temperature ranged between normal and 100°F. except for a rise to 104.2°F. on the forty-second hospital day. There continued to be bleeding from the cholecystostomy wound associated with occasional pain in the upper abdomen that radiated to the back. After the pain occurred there was expulsion of blood through the cholecystostomy wound. Beginning on the fourteenth postoperative day there were numerous episodes of melena or hematemesis or both associated with marked jaundice and bleeding from the cholecystostomy wound. When the bleeding was profuse the gall bladder became distended, and there was associated biliary colic. Between these episodes the jaundice regressed. The hemoglobin fell to 6.3 gm. per 100 ml. on the fourteenth postoperative day and, in spite of numerous transfusions, ranged between 5.8 and 9.5 gm. per 100 ml. An intravenous cholangiogram on the forty-seventh postoperative day showed the common bile duct and the hepatic duct to be poorly outlined; there appeared to be no dilatation of the opacified structures; no calculi were seen, and there was no evidence of obstruction. On the fifty-fifth postoperative day profuse bleeding from the cholecystostomy recurred.

The patient was given transfusions of blood, and an operation was performed on the next day.

Differential Diagnosis

Dr. Claude E. Welch*: It might be well to consider this case a question of "hemobilia" and to discuss the various causes of it. This is a rare syndrome. A few years ago Kerr et al.[1] presented before the Southern Surgical Society a case with massive hemorrhage from the biliary tract. He was able to collect less than 100 cases of this syndrome from the literature. Its causes are what we are interested in today. They may be divided into three groups: those that originate from the liver, from the bile ducts and from the gall bladder. In addition it can be due to a blood dyscrasia or some similar disease, of which there was no evidence in the case under discussion. Among the diseases in which hemorrhage arises from the liver are acute yellow atrophy, a post-traumatic lesion, aneurysm of the hepatic artery and tumor. Those originating from the bile ducts involve carcinoma, duodenal ulcer, portal hypertension and aneurysm. Those originating from the gall bladder are due to calculus, ulcer, carcinoma, hemorrhagic cholecystitis or a very rare disease, cholecystitis glandularis proliferans.

The illness began nine months before admission. The history was typical of acute cholecystitis, probably with common-duct obstruction because of the presence of jaundice. The patient was then well for nine months. The fact that she had severe abdominal pain nine months before entry and yet continued to be well for such a long period thereafter makes me rule out aneurysm of the hepatic artery and carcinoma, which should have produced rapid deterioration. The symptoms before admission were not typical of blood loss.

The history of septicemia caused by *Staph. albus* may be of some significance. *Staph. albus* septicemia may lead to endocarditis, which in turn may produce hepatic emboli from a mycotic aneurysm of the hepatic artery. This course of events sounds somewhat improbable.

On examination a tender mass about 10 cm. in diameter was found. I assume that this was described by the surgeon who did the cholecystostomy: a 10-cm. mass produced by the gall bladder is certainly a very large one. The remainder of the physical examination was not remarkable except for the hypertension, which might be advanced as evidence in favor of a vascular accident.

The laboratory work is remarkable chiefly for the high retention of the bromsulfalein. That, I believe, I can disregard in view of the liver biopsy. There is no mention about whether or not platelets were present in the smear, but I think it is clear that nobody worried about a blood dyscrasia, and I doubt if I need consider it seriously because all the bleeding was from one site.

I assume that the surgeon thought when he operated on the patient that the diagnosis was fairly clear — acute cholangitis and gallstones. I shall assume that he examined the area carefully so that if a good-sized aneurysm of the hepatic artery or a large hemangioma or a metastatic tumor of the liver had

*Visiting surgeon, Massachusetts General Hospital.

been present he would have found it. The calculi were removed, and the biopsy of the liver showed minimal focal chronic cholangitis. The liver biopsy provided the first (and minimal) evidence in favor of common-duct disease. The slight jaundice noted previously was not significant; therefore, in trying to locate the source of the bleeding, I shall have to say that there was not much evidence that it was in the common duct itself.

Nine days later blood oozed from the tube. This was obviously a shock to all concerned, and the thought that it was the result of trauma from the tube was soon dispelled when the patient began to bleed after the tube was removed and continued to have episodes of bleeding. She was given every chance to recover spontaneously but failed to do so. Finally, an intravenous cholangiogram was taken, and another operation performed. The cholangiogram is worthy of comment because it showed the common bile duct to be poorly outlined, but no dilatation and no calculi were seen. That is helpful information in an attempt to place the exact point of bleeding. The lack of dilatation is the more important because if the patient had carcinoma of the ampulla of Vater it would be only reasonable to suppose that she would have had marked dilatation of the common duct as well as of the gall bladder. On the intravenous cholangiogram, the finding most characteristic of obstruction or stone at the ampulla is dilatation. It is interesting that in a recent series of intravenous cholangiograms that were reported from the Lahey Clinic,[2] of 14 patients who had common-duct stones found at operation, in 7 they were overlooked on cholangiograms. In all these patients in whom stones were not visualized there was dilatation of the common duct. Therefore, the lack of dilatation of the common duct in the case under discussion is important evidence pointing away from common-duct disease as the cause of bleeding.

Where was the bleeding point — in the liver, in the gall bladder or in the common duct? Which one of the various lesions was causing it? I am inclined to say that it was not a tumor. If it had been a carcinoma, the clinical course would have been progressive in nine months, and the manifestations of the bleeding would have been less leisurely. I do not think it was papilloma or a benign tumor because, with the exception of hemangioma, no papillomas or other benign tumors have been recorded in the literature as the source of massive hemorrhage. The next consideration is a stone — by far the commonest cause of bleeding. Where would a stone have been located? On the basis of the discussion that I have mentioned, it was probably in the base of the cystic duct rather than in the common duct; the cystic duct would have been eroded by the stone, and massive hemorrhage would have resulted. I am inclined to place the lesion in the gall bladder itself and say that it was ulceration secondary to the presence of a stone. I hope that the surgeon was able to discover what the lesion was at the time of the operation because that is not always as easy as it sounds.

Dr. Benjamin Castleman: Dr. Bartlett, have you a comment?

Dr. Marshall K. Bartlett: Was bile drainage during the postoperative period mentioned? I think that information would help somewhat.

Dr. Richard B. Cohen: There was a certain amount of bile drainage after the cholecystostomy, but the quantities were difficult to estimate because of admixture of blood and, at times, frank hemorrhage.

Dr. Welch: Do you know the size of the stone? Small stones are much more likely to produce hemorrhage than one large one.

Dr. Cohen: The stones varied from several centimeters down to a very small size.

Dr. Edward D. Churchill: In view of the hematemesis, would you place that stone in an abscess near the ampulla?

Dr. Welch: I do not believe it is necessary. I remember 2 patients with hemorrhagic cholecystitis who vomited blood as a first symptom.

Dr. Richard Schatzki: The patient may have been bleeding from a duodenal ulcer.

Dr. Welch: That cannot be completely ruled out. If she was bleeding from a duodenal ulcer that perforated into the common duct, the bleeding would have been into the gastrointestinal tract and into the biliary tree simultaneously. If that were the case, the gastrointestinal tract should easily accept the blood, but not enough blood should remain in the common duct to produce jaundice. It seems to me that the bleeding was into a closed system and built up enough pressure to produce jaundice.

Dr. Richard H. Sweet: Do you think that the type of bleeding with cholecystitis that the late Dr. Franklin W. White[3] talked about was present here?

Dr. Welch: I am glad you mentioned that. He collected a series of cases with bleeding as the result of cholecystitis and stones only.

A Physician: On which side was the deformity of the second portion of the duodenum reported in the gastrointestinal series?

Dr. Wang: The deformity was on the right side.

Clinical Diagnosis

? Carcinoma of gall bladder.

Dr. Claude E. Welch's Diagnosis

Cholelithiasis, with ulceration of the gall bladder and hemobilia.

Anatomical Diagnoses

Cholecystitis glandularis, with cholelithiasis.
Biliary hemorrhage into intestinal tract.

Pathological Discussion

Dr. Castleman: At the second operation the gall bladder was removed. Did the surgeon explore the common duct?

Dr. Cohen: I do not believe so.

Dr. Castleman: We found no stones left in the bladder, but it was full of blood. Microscopically, the mucosa had a polypoid arrangement. In some places the glands extended almost to the serosa. This appearance fits the picture sometimes called cholecystitis glandularis caused by chronic infection with distention of the glands. The mucosa was quite atrophic in areas. In the areas of the tunica propria where the mucosa had ulcerated and then healed, the blood vessels were markedly distended, and there was actually free blood extending up to the surface from the distended capillaries. I believe that Dr. Welch was correct when he said that the bleeding came from a chronic cholecystitis with irritation to the mucosa by the stones. It has been said that this does not occur unless marked arteriosclerosis is present. In the case under discussion the larger vessels in the serosa of the gall bladder were arteriosclerotic, but we see that so often that I cannot claim it as a factor. In a series of 100 cases of cholecystitis and hemorrhage recently reported from the Beverly Hospital,[4] 3 out of 13 had stones; the patients who were operated on had hemorrhage within the gall bladder very similar to that in this case. One might ask why this patient continued to bleed after the stones were removed; I think that there was so much chronic infection that the bleeding did not subside. We found no evidence of carcinoma; we looked for that carefully.

Dr. Churchill: Why was the hemorrhage episodic?

Dr. Castleman: Why is any hemorrhage episodic?

Dr. Churchill: Usually because it is from an artery. Episodic hemorrhage is likely to come from a vessel of fair size and not from a mucous membrane.

Dr. Castleman: I do not believe that holds all the time. I am sure that we have seen episodic bleeding without finding a large vessel as a cause of it.

Dr. Alfred Kranes: Episodic hemorrhage is seen in gastritis.

A Physician: At the operation was it considered necessary to rule out, by exploration of the common duct, the possibility that blood was not coming from above?

Dr. Castleman: I do not know.

Dr. Welch: Is the patient well now?

Dr. Castleman: The patient is perfectly well four months after operation and has not bled.

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14. Bookplate of Charles Goddard Weld, who was instrumental in the founding of the Gay and Weld wards at the Massachusetts General Hospital.

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NEW TWIST TO AN OLD CONTROVERSY

IT is an old tradition in the United States for a new medical school to be greeted with pronounced lack of enthusiasm by the local medical profession. The reception is likely to be coolest when the organization of a teaching hospital in a small community upsets established patterns of medical practice. The establishment of the four-year medical school of the University of Mississippi at Jackson is the most recent example.

The delegates from Mississippi at the American Medical Association convention in Miami in December, 1954, clearly indicated their disapproval of the policies of the new school and centered their attack on the method by which the University proposed to remunerate its full-time clinical professors. The method involved allowing the full-time clinical professors to earn a limited and specified amount of their income over and above the salary paid by the University from private practice on patients in the University hospital. This scheme was hotly attacked as unfair practice, putting the state into the private practice of medicine, providing "a tax-paid multimillion dollar workshop for clinicians."

In response to a resolution introduced by the Mississippi delegation a committee of the American Medical Association was named to make a study of problems related to clinical faculty appointments and the private practice of medicine. An interim report from this committee based on returns from questionnaires sent to medical deans, and state and county medical societies, was presented at the Annual Congress on Medical Education and Licensure in Chicago in February. The figures indicate that the practice under criticism is standard for most of the medical schools in this country. They show that in all the government schools and in all but a few private schools the amount of private practice permitted is strictly limited. Interestingly enough a large majority of the deans were of the opinion that provision for private practice for the so-called full-time faculty improves teaching and research. Most important, all but a few considered supplementation of fees from private practice as "very necessary" to attract and retain competent full-time teachers.

The replies from the county and state medical societies indicate that the majority approve the private practice of medicine by faculty members, are of the opinion that control of the private practice of medicine by the teaching institution is adequate and do not believe that the local medical society should assist in formulating medical-school policies. However, reassuring as the over-all picture may be it is obvious that there are a few local spots where all is not bright. These trouble spots must not be allowed to threaten the whole structure of medical education. There are those in the medical profession who would use the full-time controversy to recapture control of the medi-

cal schools, which was yielded to the universities a half-century ago. This would be a sorry day indeed for those who have labored to lift medical education out of the rut of vocational training.

Perhaps the most constructive use of the committee report would be to analyze the situations where medical schools and local medical societies enjoy the most cordial and co-operative relations and to see if certain principles could not be derived that would be generally applicable. A panacea that will banish the growing pains of infant medical schools is not to be expected but at least the successful experience of others may make the problem child appear to be not so much of a problem after all.

Possibly the greatest danger in such controversies is losing sight of the one reason for the existence of medical schools and hospitals and professors and private practitioners as well. This is and must always be the care of the patient through the agencies and by the methods that best serve this purpose. Under no circumstances can the physician afford even the appearance of putting any personal considerations above that obligation.

ALPHABET SOUP

ALTHOUGH there is more fancy than fact in the claim that the late New Deal (N.D.) actually initiated the current cryptogrammic avalanche of initials (CCAI) as part of the retooling of man's efforts at communication, it has certainly given it impetus. Abbreviation as a useful adjunct in the streamlining of grammatical composition goes back to antiquity if not beyond, Homer himself having been one of the first to employ the familiar B.C. as an identification of the period in which he lived and sang. It is only in recent years and under the combined influence of politics and science that the verbal stripdown has assumed the character of a striptease. Thus b.c. when not capitalized is credited by Mr. Webster, the American lexicographer (A.L.), as officially representing both bass clarinet and boat club, although the less remote A.D. stands alone in meaning, as it properly should.

Initials have their legitimate uses, their acceptance without too great and persistent protest (G.P.P.) representing the criterion of legitimacy. Historically, or at least in English history, ER stands appropriately for any number of Edward Reges up to eight, or for Elizabeth Regina (prima or secunda); ERV, however, is not projected to the fifth female monarch (F.F.M.) of that name, meaning simply English Revised Version. Initials are legitimately used for orders, institutions and degrees, with some overlapping. Considering the A's alone one finds that the triple linking represents Agricultural Adjustment Administration, Amateur Athletic Association, American Automobile Association, Automobile Association of America and Antiaircraft Artillery — it all depends on the context; the addition of a fourth letter widens the scope to American Academy of Arts and Letters (AAAL) and/or, as the cryptophiles insist on putting it, American Academy of Arts and Sciences and American Association for the Advancement of Science (AAAS).

A.F.A.M. as well as A.F. & A.M. signify the Ancient Free and Accepted Masons; A.A.U. the Amateur Athletic Union and A. A. U. P. the American Association of University Professors. In case the sweet uses of the A, not necessarily representing Adversity, produce a slight swimming of the senses (S.S.S.) one may consider the second letter of the alphabet, which in its splendid isolation is taken variously and officially, capitalized or in lower case, to stand for bacillus, Bible, bishop (in chess), boron (in chemistry), Boston, British, Brotherhood, bachelor, base, bass, basso, bat, battery, bay, biscuspid, bolivar, book, born, breadth and brother. Commercially, B/ — is bag or bale. And so it goes, t.n.t.m. (too numerous to mention).

Events within the memory of living man, however, seem to have conspired in the production of the present RAT (Reign of Alphabetic Terror), when no one knows WHO's hand is turned against him, or why. And in reference to WHO, an intriguing "Union S.O.E." turned up in a report of that worthy organization and for months has defied the most ardent efforts at identification. Time saving forsooth! As indicated earlier in the present anthology, the CCAI started with the ND or even as a DP (depression plant). It has not since then been relinquished by politics, statesmanship or social welfare, as witness those exasperating offspring of the U.N. — UNICEF and UNESCO — whose meanings repeatedly slip from the grasp of the most retentive memory, especially when otherwise occupied.

Each specialty, each A.I.E. (Area of Intellectual Enterprise) has its protective jargon and its quick corner-cuttings ostensibly designed to improve the C.I.* but serving actually to frustrate the reader and erect between the author and himself a wall of irritated distrust. In science and especially in medicine, the most prolific and perhaps the least articulate division of science, the mania for crisp consonants seasoned with a profusion of appropriate vowels with or without a peppering of interspersed periods has reached its height.

Many of these abbreviations have become usefully integrated into the speech and literature of the profession; such are BMR and EKG, rbc and wbc and, more recently, ACTH. They are, however, abbreviations for all their acceptance and consequently not to be employed in every literary context. Accretions to this rather risky and generally undesirable vocabulary should be accepted with caution. One manu-

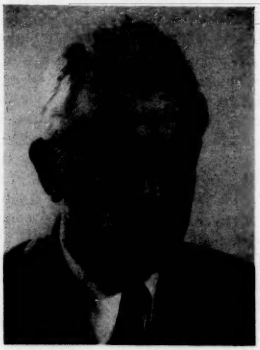
*Comprehension Index.

script submitted to the *Journal* proposes S.L.E for *systemic* lupus erythematosus and another contains as its author's contribution to brevity, if not to clarity, EH for enlarged heart, HF for heart failure, ASHD for aortic stenotic heart disease, PAT for paroxysmal atrial tachycardia, AF for atrial fibrillation, RBBB for right-bundle-branch block and others t.n.t.m.

There is urgency enough in today's catch-as-catch-can culture for quick delivery whether of ideas or of laundry, but not quite the urgency that legitimately inspired the abbreviations used by the hieroglyphic amanuensis trying to get a quick note off by the afternoon bullock cart. And so far as economy in both time and space is concerned, it can be better served by w.o. (writing out) more words and using fewer of them.

DR. PETER PINEO CHASE

BOTH medical journalism and science writing have lost, by the death of Dr. Peter Pineo Chase, of Prov-



idence, one who may be considered the dean of each of these divisions of literature. Since 1942 the editor of the *Rhode Island Medical Journal,* Dr. Chase had also for years contributed a daily health column to the Providence *Journal-Bulletin* in addition to conducting at first an active and more lately a consulting surgical practice.

Peter Chase was, in his own refreshing way, a Yankee from Olympus, and had he been discovered on the slopes of that fabled mountain when snow-clad he would probably have been on skis. For membership in the Appalachian Mountain Club constituted for Peter, as for his wife, Helen, a chief source of outdoor recreation, and the inconsequential burden of seventy years or more (he died at seventy-seven) were not permitted to interfere too greatly with the reasonable activities associated with such an organization.

As a gentler avocation Peter Pineo Chase was a student of Samuel Johnson and a member of the exclusive Johnson Society and had written about Johnson's physical and emotional infirmities and their probable effect on the great Cham's literary achievements; he had contributed to the *Journal* in 1953 a "Doctor Afield" on Samuel Gridley Howe, and as recently as April of this year a similar essay on Usher Parsons.

Although identified throughout his adult life with Rhode Island, Peter had been born in Hyannis, Massachusetts, the son of Herman and Maude Pineo Chase and the grandson of Dr. Peter Pineo, a practitioner of that town and a surgeon in the Union Army during the Civil War. Peter himself, after graduation from Brown University and Harvard Medical School and internships in the Boston Lying-in and Rhode Island hospitals, served with both the British and American armies in France before settling down permanently in Providence.

To know Peter Pineo Chase was to love, admire and respect him; he was New England, seasoned and independent; like his literary idol he was one who kept his friendships in repair.

WINNERS OF PRIZE-ESSAY COMPETITION

THE editors of the *Journal* take considerable pleasure and a degree of pride in announcing the outcome of the eighth annual student prize-essay competition, which came to its conclusion on March 15, 1956. According to the careful decision of the judges the essay of greatest merit in a field that showed considerable merit was submitted by Laurence E. Earley, of the fourth-year class of the University of North Carolina School of Medicine. His subject was "Extreme Polyuria in Obstructive Uropathy"; the paper will be published as a special article in a later issue of the *Journal,* long before which time Mr. Earley will have received a tastily embossed check for $100, suitable either for framing or for conversion into cash.

The second prize, of $25.00, was awarded to Mr. Robert J. Hubsmith, of Cornell University Medical College, for an essay on "Liver Failure with Ammonium Toxicity Following Carbon Tetrachloride Ingestion," and the third, of a two-year subscription to the *Journal,* to Mr. Thomas Ungerleider, of Western Reserve University School of Medicine, in Cleveland. Mr. Ungerleider's title was "The Significance of Pleural Effusion."

Despite the ever-increasing invasion of the field of medicine by a sex no longer (if ever) the weaker one, no woman entered this year's contest. It was the first time that women students had avoided the competition in such numbers. Also for the first time in the eight-year history of the competition, not a single entry was submitted from any of the three schools of medicine located in Boston, lending some substance to the allegation that a prophet is indeed without

honor in his own country. In other ways the *Journal* seems not to lack favor with the nation's medical students, over 7600 of whom are subscribers at the time of this writing, representing an increase of approximately 800 since the announcement of last year's prize winners was made.

It is expected that the third-year students of the 1955-1956 academic year will await with restrained eagerness the announcement next fall of the competition for 1957.

Meeting of the Mass. Med. Society—*In consequence of the Journal being put to press before the date of publication, we are unable to publish the proceedings at the annual meeting.*

Boston M. & S. J. *May 29, 1856*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BARTLETT — Bernice A. Bartlett, M.D., of Haverhill, died on January 21. She was in her sixty-eighth year.

Dr. Bartlett received her degree from Boston University School of Medicine in 1911. She was formerly pathologist at Hale and Gale hospitals.

She is survived by a sister.

BROUSSEAU — William G. Brousseau, M.D., of Cambridge, died on April 12. He was in his eighty-third year.

Dr. Brousseau received his degree from Tufts College Medical School in 1896. He was formerly city physician in Cambridge and a member of the staffs of Cambridge City, Mount Auburn and Holy Ghost hospitals. He was a fellow of the American Medical Association.

He is survived by his widow.

HERRICK — Van Buren Herrick, M.D., of Worcester, died on April 15. He was in his eighty-sixth year.

Dr. Herrick received his degree from University of Vermont College of Medicine in 1896. He was a fellow of the American Medical Association.

He is survived by a son and a daughter.

RAGLE — Benjamin H. Ragle, M.D., of Boston, died on May 1. He was in his sixty-eighth year.

Dr. Ragle received his degree from Harvard Medical School in 1916. He was a member of the staffs of the Massachusetts General and Mount Auburn hospitals, a fellow of the American Medical Association and the American College of Physicians and a member of the Association for the Study of Internal Secretions, American Heart Association and New England Heart Association.

He is survived by his widow, a daughter and three sons.

CORRESPONDENCE

A TIMELY WARNING

To the Editor: It seems to me that the most important lesson to be derived from Case 42121 in the March 22 issue of the *Journal* was not brought out in the discussion. In this particular case of a twenty-one-month-old girl brought in to the Worcester Memorial Hospital because of hematuria, an intravenous pyelogram was taken "shortly after admission," presumably before the nonprotein nitrogen in the blood was determined. It is understandable that with the severely impaired kidney function in this case (nonprotein nitrogen of 122 mg. per 100 ml.), no dye was noted in either side "during a period of two hours."

I think it should be emphasized that an intravenous pyelogram should not be attempted until the nonprotein nitrogen is determined. With retention of nonprotein nitrogen, not only will the x-ray findings be unsatisfactory, but also there is a theoretical possibility of throwing the patient into uremia by adding the additional burden of excreting a dye on functionally impaired kidneys.

As for the immediate cause of death, which was clinically diagnosed as pulmonary edema, one may quote Dr. Cabot, "I wasn't there." There was some question whether this child was receiving an intravenous infusion. A better explanation for the pathological physiology in this case is that the patient became progressively more uremic and that the increased capillary permeability of the pulmonary tree, combined with infection, gave rise to the terminal hemorrhagic bronchopneumonia.

Fortunately, the performance of the test mentioned above did not influence the final outcome, because the prognosis of a patient with bilateral Wilms tumors is universally fatal. However, it is worth repeating that one should at all times determine the value of the nonprotein nitrogen in the blood before doing an intravenous pyelogram. If it is elevated, a retrograde pyelogram can be taken, when indicated, because the information obtained by excretory urography under such conditions would be valueless, and there is always the possibility of making a uremic patient worse.

JACOB BREM, M.D.

Worcester, Massachusetts

SUSPENSION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held January 19, 1956, it was voted to suspend the registration of Dr. Oliver Holman Clarke, Myrtle Point, Oregon.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

BOOK REVIEW

Röntgenschichtverfahren: Grundlagen der technischen Entwicklung und der klinischen Anwendung für die Praxis. By Prof. Dr. R. Griesback; and Dr. F. Kemper. 4°, cloth, 143 pp., with 92 illustrations. Stuttgart: Georg Thieme, 1955. DM 39.- $9.30. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

The first half of this book on the fundamental principles underlying the technical development and clinical application of laminagraphic procedures offers a complete survey in a concise form. A short description of specialized procedures that attempt to isolate radiographically certain otherwise inaccessible parts of the body is followed by a chronologic list of all the methods and devices described up to 1954. Further details of the mathematical and physical principles are then discussed in a simple manner. An extensive chapter deals with all apparatus developed up to the present and gives a technical description and a photograph of the more important machines. These devices — of astounding and confusing variety — are clearly divided into four major types: motion with changing vectors producing blurring; linear motion producing blurring; transverse body section; and other special methods. The last group includes not only the more unusual and specialized methods but also the manifold auxiliary laminagraphic devices such as those

applied for stereoscopy, kymography, fluoroscopy, photofluorography, relief films, multilayer cassettes and serial films.

The value of this first part of the book is greatly enhanced by an extensive list of nearly 500 references, which seem to cover all major papers concerned with the technical aspect of the subject.

The clinical part deals mainly with the application of laminagraphy in lung disease. In addition to suggestions concerning their own methodical approach the authors present a list of indications divided as absolute, relative and no indication. They restrict themselves to the practically sound and approved indications, emphasizing the value and superiority of simpler radiologic approaches whenever necessary. The text is accompanied by a series of excellent radiographic reproductions.

Apart from the discussion of lung disease, which is fairly detailed though incomplete and devoid of any statistical data, there is little information regarding other clinical application. Only one page is devoted to bones, and one small paragraph to the larynx. The list of references is poor, covering little more than a dozen papers of German and Swiss origin only. No mention is made of the pioneering French, Italian and Swedish work in the clinical field, which has clearly shown the value of laminagraphy for many parts of the body.

In spite of the shortcomings of the clinical part, which contains little of interest for the trained radiologist, this book is highly recommended because of its excellent technical part, which affords a useful and logical guide through the jungle of possible and actual methods and devices, with a ready reference to the original papers. This work should stimulate deserved interest in a field that appears to have been neglected in this country.

JUSTIN HUPPE, M.D.

NOTICE

FIFTH ANNUAL SYMPOSIUM FOR GENERAL PRACTITIONERS

The Fifth Annual Symposium for General Practitioners on Tuberculosis and Other Chronic Pulmonary Disease will be held at Saranac Lake, New York, July 9-13. It is approved for twenty-six hours of formal credit for members of the American Academy of General Practice.

Sessions will be held in the various sanatoriums, hospitals and laboratories in the Saranac Lake area.

Further information may be obtained from Dr. Edward N. Packard, General Chairman, Symposium for General Practitioners, P. O. Box 262, Saranac Lake, New York.

SOCIETY MEETINGS AND CONFERENCES

MAY 28. Jewish Memorial Hospital. Page 924, issue of May 10.
MAY 28 and 29. Consultation Clinics for Crippled Children in Massachusetts. Page 868, issue of May 3.
MAY 28–JUNE 1. European Symposium on Vitamin B. Page 578, issue of September 29.
MAY 29. Boston City Hospital House Officers' Association. Page 924, issue of May 10.
JUNE 1. Massachusetts Society of Anesthesiologists. Page 968, issue of May 17.
JUNE 1–9. International Medical-Surgical Meetings. Page 540, issue of March 15.
JUNE 4–6. Third National Cancer Conference. Page 876, issue of May 3.
JUNE 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
JUNE 6–10. American College of Chest Physicians. Page 876, issue of May 3.
JUNE 7. New England Hospital Staff Clinical Conference. Page 968, issue of May 17.
JUNE 9 and 10. Society for Investigative Dermatology. Page 876, issue of May 3.
JUNE 10 and 11. American Gastroscopic Society. Page 875, issue of May 3.
JUNE 15. New England Pediatric Society. Page 924, issue of May 10.
JUNE 17. American Electroencephalographic Society. Page 924, issue of May 10.
JUNE 18–20. American Neurological Association. Page 875, issue of May 3.
JUNE 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.
JUNE 21–24. American Academy of Dental Medicine. Page 994, issue of December 1.
JULY 9–13. Fifth Annual Symposium for General Practitioners. Notice above.
AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.
SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 10–14. American Dietetic Association. Page 1180, issue of December 29.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MAY 31

THURSDAY, MAY 31
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building. Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Staff Conference. Regulation of Compound and Volume in Body Fluid. Dr. Maurice B. Strauss. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Tumors of the Lung. Dr. Harrison Black. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, JUNE 1
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.
7:30 p.m. Massachusetts Society of Anesthesiologists. After Eight Years: The present status of induced hypotension. Dr. Nicholas Greene. Harvard Club, 374 Commonwealth Avenue.

SATURDAY, JUNE 2
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JUNE 4
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.

(Concluded on page xxiv)